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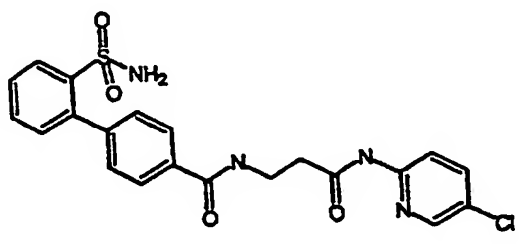
(54) Title: β-AMINO ACID-, ASPARTIC ACID- AND DIAMINOPROPIONIC-BASED INHIBITORS OF FACTOR Xa



(57) Abstract: Novel β-amino acid-, aspartic acid- and diaminopropionic-based compounds of the general formula A-Q-D-E-G-J-X wherein A, Q, D, E, G, J and X have the meanings given in the description, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

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β-AMINO ACID-, ASPARTIC ACID- AND DIAMINOPROPIONIC - BASED INHIBITORS OF FACTOR Xa

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel β-amino acid-, aspartic acid- and diaminopropionic-based factor Xa-inhibiting compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by undesired thrombosis or coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5,

411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino

Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, *"Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naphthyl group via a straight or branched chain alkylene,-C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds are needed which selectively or preferentially bind to Factor Xa. Compounds with a higher affinity for binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability or other pharmacologically desirable properties.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of undesired thrombosis or blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or coagulation disorders. For example, compounds of the invention can be used in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation. Compounds of the invention may also be used to inhibit coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents. In one embodiment, the present invention provides compounds comprising a bridging group which is a member selected from the group consisting of β-amino acids, aspartic acids and diaminopropionic acids. Particular embodiments of the compounds of the present invention are set forth below as preferred embodiments and include all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the compounds and pharmaceutical compositions of the invention for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation

process in mammals, or for preventing coagulation in biological samples such as, for example, stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkynyl" refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkynyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure " and " C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three

rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from lower alkoxy, lower alkyl, lower alkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, lower alkylphenyl, naphthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group

consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocyclic and bicyclic heterocyclic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocyclic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred

organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

The invention provides a compound of the formula:

A-Q-D-E-G-J-X

wherein:

A is a member selected from the group consisting of:

(a) phenyl which is substituted with 0-3 R^1 groups;

(b) naphthyl, which is substituted with 0-3 R^1 groups; and

(c) an aromatic or non-aromatic 5-10 membered heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4

heteroatoms selected from N, O and S and is substituted with 0-2 R^1 groups;

R^1 is a member selected from the group consisting of:

halo, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -NO_2, -$(CH_2)_m$-NR^2R^3, -NHR^2R^3, -$C(=O)$-NR^2R^3, -$C(=O)$-OR^2, -$S(=O)_2$-NR^2R^3, -$S(=O)_2$-R^2, -CF_3, -$(CH_2)_m$-OR^2, a carbocyclic aryl group and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^2 and R^3 are independently selected from:

H, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and -C_{0-6}alkyl-(carbocyclic aryl), or R^2 and R^3 together with the N atom to which they are attached can form a 5 to 8 membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -CF_3 and -NO_2;

m is an integer of 0-3;

Q is a member selected from the group consisting of:

a direct link; divalent C_1-C_4alkyl; divalent C_2-C_4alkynyl; divalent C_{2-4}alkenyl; -$C(=O)$-; -$C(=N$-$R^4)$-, -$N(-R^4)$-, -NR^4-CH_2-, -$C(=O)$-$N(-R^4)$-, -$N(-R^4)$-$C(=O)$-, -$S(=O)_2$-, -O-, -$S(=O)_2$-$N(-R^4)$- and –$N(-R^4)$-$S(=O)_2$-, wherein one or more hydrogens on each of the divalent C_1-C_4alkyl, divalent C_2-C_4alkynyl and divalent C_{2-4}alkenyl moieties can be replaced with a -R^4 group;

R^4 is a member selected from the group consisting of:

H, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and -C_{0-6}alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -CF_3 and -NO_2;

D is a member selected from the group consisting of:

(a) phenyl substituted with 0-2 R^{1a} groups; and

(b) an aromatic or non-aromatic 5-10 membered heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and the ring system is substituted with 0-2 R^{1a} groups;

R^{1a} is a member selected from the group consisting of:

halo, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -NO_2, -$(CH_2)_n$-$NR^{2a}R^{3a}$, -$S(=O)_2NR^{2a}R^{3a}$, -$S(=O)_2$-R^{2a}, -CF_3, -$(CH_2)_n$-OR^{2a}, -C(=O)-O-R^{2a}, -$C(=O)NR^{2a}R^{3a}$, and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S and -C_{0-6}alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the aromatic heterocyclic ring and the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -CF_3 and -NO_2;

n is an integer of 0-2;

R^{2a} and R^{3a} are independently a member selected from the group consisting of:

H, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and -C_{0-6}alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -CF_3 and -NO_2;

E is selected from:

-$(CH_2)_q$-C(=O)-, -$(CH_2)_q$-NR^5-C(=O)-$(CH_2)_x$-, -$(CH_2)_q$-C(=O)-NR^5-$(CH_2)_x$-, -$(CH_2)_q$-NR^5-CO-$NR^6(CH_2)_x$-, and -SO_2-;

q and x are independently an integer of 0-2;

R^5 and R^6 are independently a member selected from the group consisting of:

H, -C_{1-6}acyl, -C_{1-6}alkyl, -C_{1-6}alkyloxy, -C_{1-6}alkyl-C(=O)-$NR^{2b}R^{3b}$, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-6}alkylC_{3-8}cycloalkyl, -C_{1-4}alkyl-C(=O)-OH, -C_{0-6}alkyl-(carbocyclic aryl), -C_{0-4}alkyl-(monocyclic heteroaryl) and -C_{1-4}alkyl-C(=O)-O-C_{1-4}alkyl, wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety and the monocyclic heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$OH, -CN, -CF_3 and -NO_2;

R^{2b} and R^{3b} are independently a member selected from the group consisting of:

H, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and -C_{0-6}alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -CF_3 and -NO_2;

G is $-CHR^6-$ and $-CHR^6-CHR^7-$;

R^6 and R^7 are each a member independently selected from the group consisting of:

H, alkyl, $-C_{0-2}$-alkyl-aryl, $-C_{0-2}$-alkyl-heteroaryl, $-C_{0-2}$-alkyl-$C(=O)-OR^8$; $-C_{0-2}$-alkyl-$C(=O)-NR^9R^{10}$; $-C_{0-2}$-alkyl-OR^9; $-C_{0-2}$-alkyl-O-C_{0-2}-alkyl-OR^9; $-C_{0-2}$-alkyl-O-C_{0-2}-alkyl-NR^9R^{10}; $-C_{0-2}$-alkyl-NR^9R^{10}; $-C_{0-2}$-alkyl-$NR^9-C(=O)-R^{10}$; $-C_{0-2}$-alkyl-$NR^9-C(=O)-O-R^{10}$; $-NR^9-C(=O)-C_{0-2}$-alkylaryl; $-C_{0-2}$-alkyl-$NR^8-C(=O)-NR^9R^{10}$, $-C_{0-2}$-alkyl-$NR^9-SO_2R^{10}$; and $-C_{0-2}$-alkyl-$NR^8-SO_2NR^9R^{10}$;

R^8, R^9 and R^{10} are each a member independently selected from the group consisting of:

H, $-C_{1-4}$-alkyl, $-C_{0-4}$-alkyl-carbocyclic aryl; $-C_{0-4}$-acyl; $-C_{0-4}$-alkyl-heterocycle; and R^8 with R^9 and R^9 with R^{10}, together with the N atom to which they are attached may each independently form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

halo, $-C_{1-4}$-alkyl, $-CN$, $-NO_2$, $-C(=O)-NR^{2d}R^{3d}$, $-C(=O)-OR^{2d}$, $-(CH_2)_t-NR^{2d}R^{3d}$; $-SO_2-NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$ and $-(CH_2)_t-OR^{2d}$;

t is an integer from 0-3;

R^{2d} and R^{3d} are each independently a member selected from the group consisting of:

H, $-C_{1-4}$-alkyl and $-C_{1-4}$-alkyl-aryl;

J is a member selected from the group consisting of:

$-C(=O)-N(-R^{11})-$; $-N(-R^{11})-C(=O)-$ and $-N(-R^{11})-SO_2-$;

R^{11} is a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups;

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) a fused aromatic heterobicyclic ring system containing 1-4 heteroatoms selected from N, O and S and having 0-3 ring atoms substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; -C_{1-4}-alkyl; carbocyclic aryl; -CN; -C(=O)-OR^{2e}; -C(=O)-$NR^{2e}R^{3e}$; -NO_2; -$NR^{2e}R^{3e}$; -CH_2-$NR^{2e}R^{3e}$; -SO_2-$NR^{2e}R^{3e}$; -SO_2-R^{2e}; -CF_3; -OR^{2e}; -O-CH_2-C(=O)-OR^{2e}; -NR^{2e}-C(=O)-R^{3e}; -N(-R^{2e})-SO_2-R^{3e}; -CH_2-N(-R^{2e})-C(=O)-R^{3e} and -CH_2-N(-R^{2e})-SO_2-R^{3e};.

R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{2c} and R^{3c} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} is a member selected from the group consisting of:

halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-$NR^{2g}R^{3g}$; -C(=O)-OR^{2g}; -NO_2; -$(CH_2)_s$-$NR^{2g}R^{3g}$; -$SO_2NR^{2g}R^{3g}$; -SO_2R^{2g}; -CF_3; and -$(CH_2)_s$$OR^{2g}$;

s is an integer from 0-3;

R^{2g} and R^{3g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and pro-drug derivatives, thereof.

The invention provides a compound of the formula:

A-Q-D-E-G-J-X

wherein:

A is a member selected from the group consisting of:

(a) phenyl, which is substituted with 0-2 R^1 groups;

(b) naphthyl, which is substituted with 0-2 R^1 groups; and

(c) an aromatic or non-aromatic heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring system which is substituted with 0-2 R^1 groups;

R^1 is a member selected from the group consisting of:

halo; C_{1-4}-alkyl; a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-NR^2R^3; -C(=O)-OR^2; -NO_2; -$(CH_2)_s$-NR^2R^3; -$SO_2NR^2R^3$; -SO_2R^2; -CF_3; and -$(CH_2)_sOR^2$;

R^2 and R^3 are each independently selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl; or R^2 and R^3 together with the N atom to which they are attached can form a 5 to 8 membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S;

m is an integer of 0-2;

Q is a member selected from the group consisting of:

a direct link; a divalent C_1-C_4-alkyl group; a divalent C_2-C_4-alkynyl group; a divalent C_2-C_4-alkenyl group; -C(=O)-, -C(=N-R^4)-; -N(-R^4)-, -N(-R^4)-CH_2-; -C(=O)-N(-R^4)-; -N(-R^4)-C(=O)-, -SO_2-, -O-, -SO_2-N(-R^4)- and –N(-R^4)-SO_2-;

R^4 is a member selected from the group consisting of:

H, -C_{1-4}-alkyl and -C_{0-4}-alkyl-(carbocyclic aryl);

D is a member selected from the group consisting of:

(a) phenyl substituted with 0-2 R^{1a} groups; and

(b) an aromatic or non-aromatic 5-6 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms on the heterocyclic ring are substituted with 0-2 R^{1a} groups;

R^{1a} is a member selected from the group consisting of:

halo, -C_{1-4}-alkyl, -CN, -NO_2, -C(=O)-$NR^{2a}R^{3a}$, -C(=O)-OR^{2a}; -$(CH_2)_n$-$NR^{2a}R^{3a}$; -SO_2-$NR^{2a}R^{3a}$; -SO_2R^{2a}; -CF_3 and -$(CH_2)_n$-OR^{2a};

n is an integer from 0-2;

R^{2a} and R^{3a} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-(carbocyclic aryl);

E is a member selected from the group consisting of:

-C(=O)-N(-R^5)- and –N(-R^5)-C(=O)-;

R^5 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkyl-(carbocyclic aryl); -C_{0-4}-alkyl-(monocyclic heteroaryl); -C_{1-4}-alkyl-C(=O)-OH; -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl; and

$-C_{1-4}$-alkyl-C(=O)-$NR^{2b}R^{3b}$;

R^{2b} and R^{3b} are each a member independently selected from the group consisting of: H, $-C_{1-4}$-alkyl, $-C_{0-4}$-alkyl-aryl; $-C_{0-4}$-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:
Halo; $-C_{1-4}$-alkyl; -CN, $-NO_2$; -C(=O)-$NR^{2c}R^{3c}$; -C(=O)-OR^{2c}; $-(CH_2)_m$-$NR^{2c}R^{3c}$; $-SO_2$-$NR^{2c}R^{3c}$; $-SO_2R^{2c}$; $-CF_3$ and $-(CH_2)_m$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:
H; $-C_{1-4}$-alkyl; and $-C_{1-4}$-alkyl-aryl;

G is $-CHR^6$-CHR^7-;

R^6 and R^7 are each a member independently selected from the group consisting of:
H; alkyl; $-C_{0-2}$-alkyl-aryl; $-C_{0-2}$-alkyl-heteroaryl; $-C_{0-2}$-alkyl-C(=O)-OR^8; $-C_{0-2}$-alkyl-C(=O)-NR^9R^{10}; $-C_{0-2}$-alkyl-O-R^9; $-C_{0-2}$-alkyl-O-C_{2-4}-alkyl-O-R^9; $-C_{0-2}$-alkyl-O-C_{2-4}-alkyl-NR^9R^{10}; $-C_{0-2}$-alkyl-NR^9R^{10}; $-C_{0-2}$-alkyl-N(-R^9)-C(=O)-R^{10}; $-C_{0-2}$-alkyl-N(-R^9)-C(=O)-OR^{10}; $-C_{0-2}$-alkyl-N(-R^8)-C(=O)-NR^9R^{10}, $-C_{0-2}$-alkyl-N(-R^9)-SO_2-R^{10}; and $-C_{0-2}$-alkyl-N(-R^8)-SO_2-NR^9R^{10};

R^8, R^9 and R^{10} are each a member independently selected from the group consisting of:
H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-C_{0-4}$-alkyl-heterocycle; and R^9 with R^{10}, together with the N atom to which they are attached may each independently form a 5-8 membered heterocyclic ring containing 1-4

heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN; -NO_2; -C(=O)-$NR^{2d}R^{3d}$; -C(=O)-OR^{2d}; -$(CH_2)_t$-$NR^{2d}R^{3d}$; -SO_2-$NR^{2d}R^{3d}$; -SO_2R^{2d}; -CF_3 and -$(CH_2)_t$-OR^{2d};

t is an integer from 0-2;

R^{2d} and R^{3d} are each independently a member selected from the group consisting of:

H, -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

J is a member selected from the group consisting of:

-C(=O)-N(-R^{11})-; -N(-R^{11})-C(=O)- and –N(-R^{11})-SO_2-;

R^{11} is a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups;

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) a fused aromatic heterobicyclic ring system containing 1-4 heteroatoms selected from N, O and S and having 0-3 ring atoms substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-CN; -C_{0-2}-C(=O)-OR^{2e}; -C_{0-2}-C(=O)-$NR^{2e}R^{3e}$; -C_{0-2}-NO_2; -C_{0-2}-$NR^{2e}R^{3e}$; -CH_2-$NR^{2e}R^{3e}$; -C_{0-2}-SO_2-$NR^{2e}R^{3e}$; -C_{0-2}-SO_2-R^{2e}; trihaloalkyl; -C_{0-2}-OR^{2e};

$-O-CH_2-C(=O)-OR^{2e}$; $-C_{0-2}-N(-R^{2e})-C(=O)-R^{3e}$; $-C_{0-2}-N(-R^{2e})-SO_2-R^{3e}$; $-CH_2-N(-R^{2e})-C(=O)-R^{3e}$ and $-CH_2-N(-R^{2e})-SO_2-R^{3e}$;.

R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{1-4}$-alkyl-carbocyclic aryl; $-C_{1-4}$-alkyl-heterocyclic; and R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} is a member selected from the group consisting of:

halo; $-C_{1-4}$-alkyl; a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; $-C(=O)-NR^{2g}R^{3g}$; $-C(=O)-OR^{2g}$; $-NO_2$; $-(CH_2)_s-NR^{2g}R^{3g}$; $-SO_2NR^{2g}R^{3g}$; $-SO_2R^{2g}$; $-CF_3$; and $-(CH_2)_sOR^{2g}$;

s is an integer from 0-2;

R^{2g} and R^{3g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and $-C_{0-4}$-alkyl-carbocyclic aryl;

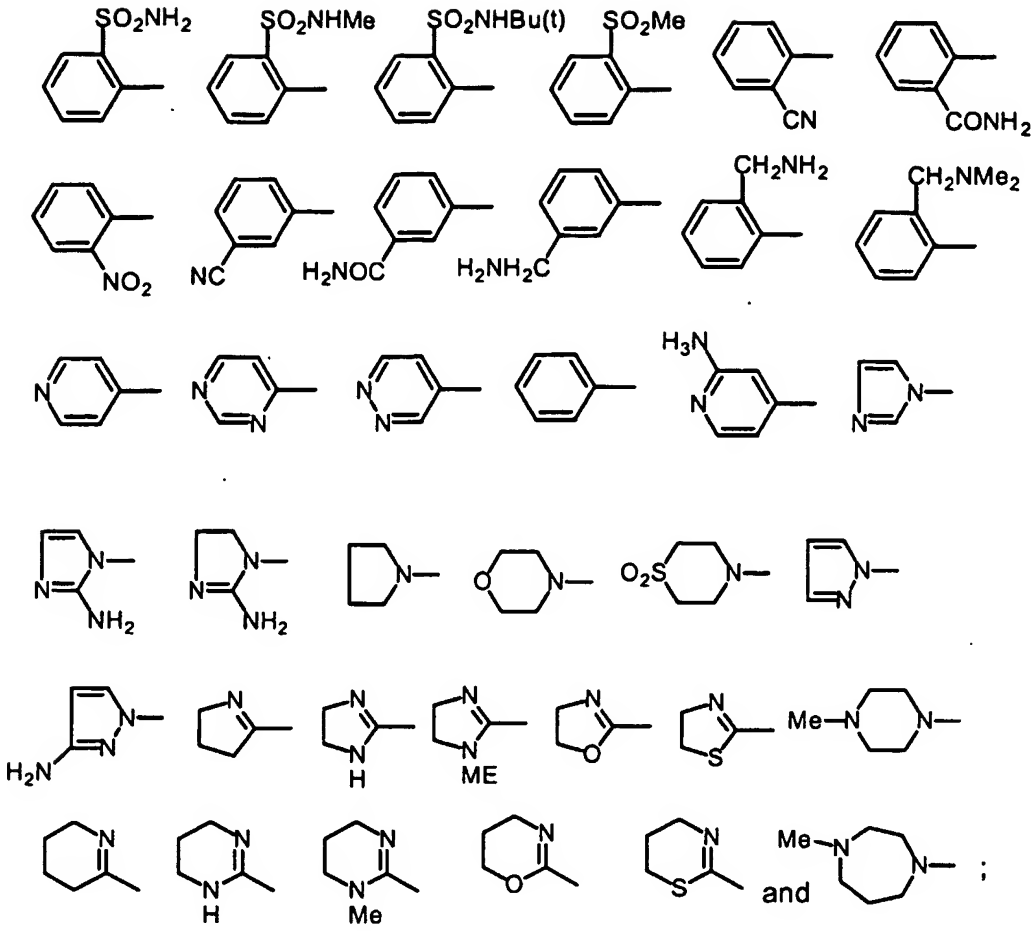
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a preferred embodiment the invention provides a compound of the formula:

A-Q-D-E-G-J-X

wherein:

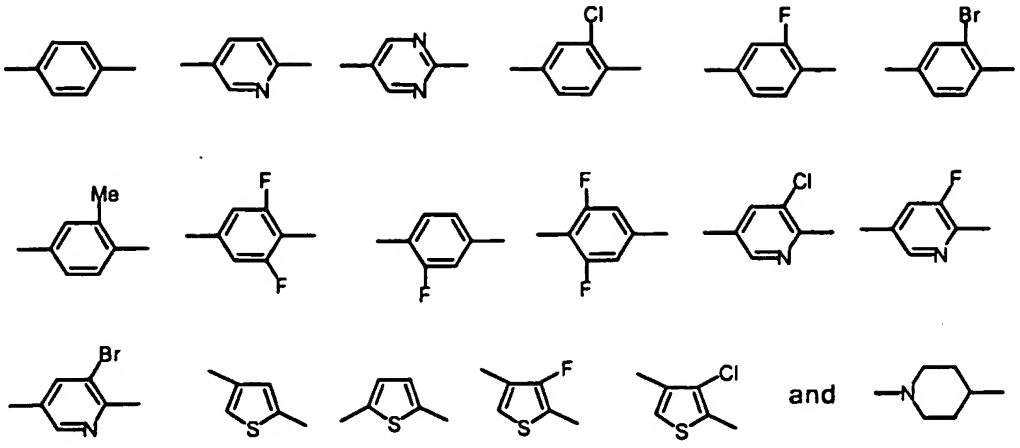
A is a member selected from the group consisting of:



Q is a member selected from the group consisting of:

a direct link; -C(=O)-; -N(CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-; and -CH_2-;

D is a member selected from the group consisting of:

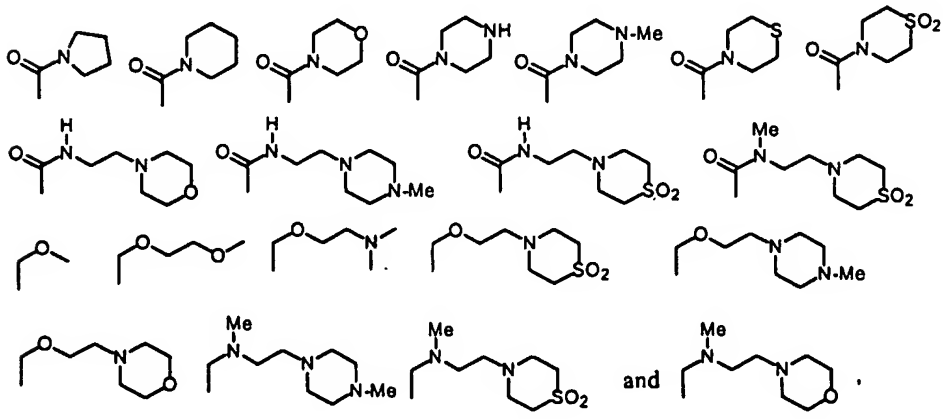


E is a member selected from the group consisting of:

-NH-C(=O)- and -C(=O)-NH-;

G is $-CHR^6-CHR^7-$, wherein R^6 and R^7 are each independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$; $-(CH_2)_2-COOH$; -COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-NH_2$; -NH-Ac, -NH-C(=O)-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bn; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; $-NH-SO_2-Me$; $-NH-SO_2-Bu$; $-NH-SO_2-Ph$; $-NH-SO_2-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-O-Ac$;



J is a member selected from the group consisting of:

-C(=O)-NH-; -NH-C(=O)-; and -NH-SO_2-;

X is a member selected from the group consisting of:

(a) phenyl, which can be substituted with 0-3 R^{1c} groups;

(b) naphthyl, which can be substituted with 0-3 R^{1c} groups;

(c) pyridyl, which can be substituted with 0-3 R^{1c} groups; and

(d) pyrimidinyl, which can be substituted with 0-3 R^{1c} groups;

R^{1c} is in each occurrence independently a member selected from the group consisting of:

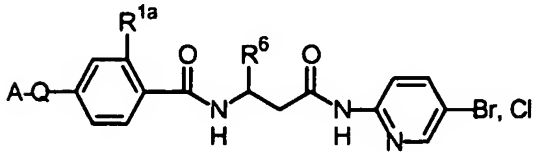
-Cl; -Br; -F; -I; -OH; -OMe; -COOH; -COOEt; -C(=O)-NH_2;

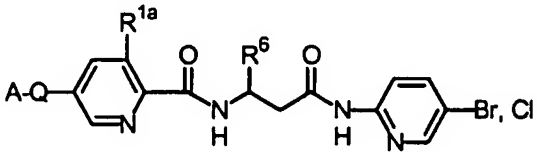
-C(=O)-NH-Me; -C(=O)-N(-Me)$_2$; -CN; -NO_2; -NH_2; -NH-Me; -CH_2-NH_2;

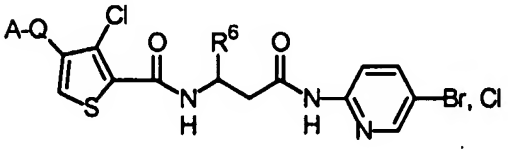
-CH_2-NH-Me; -SO_2-Me; -SO_2-NH_2; and -SO_2-NH-Me,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

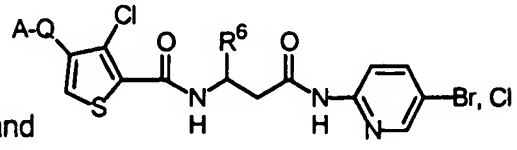
In another preferred embodiment, the present invention provides a compound of the following formulae:



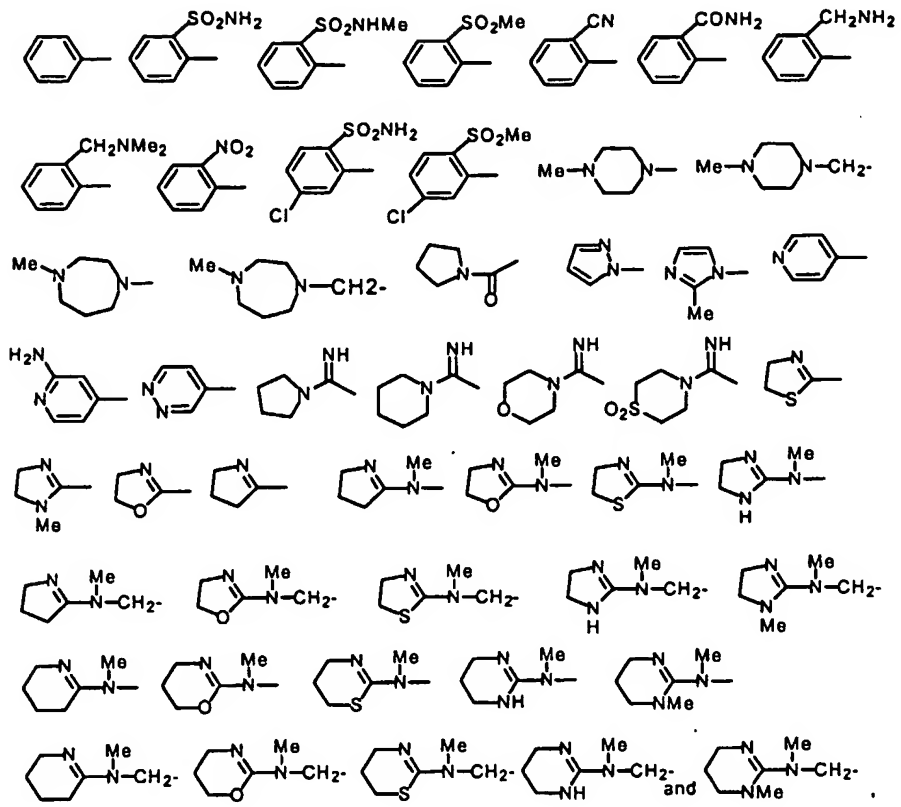




and



wherein the A-Q portion for each of the above formulae is independently a member selected from the group consisting of:



R^{1a} on the phenyl and pyridyl portions of the above formulae is independently selected from the group consisting of:

-H; -Cl; -F; -Br; -Me; -O-Me; -NO_2; -COOH; -CN; -C(=O)-NH_2; -C(=O)-O-Me;

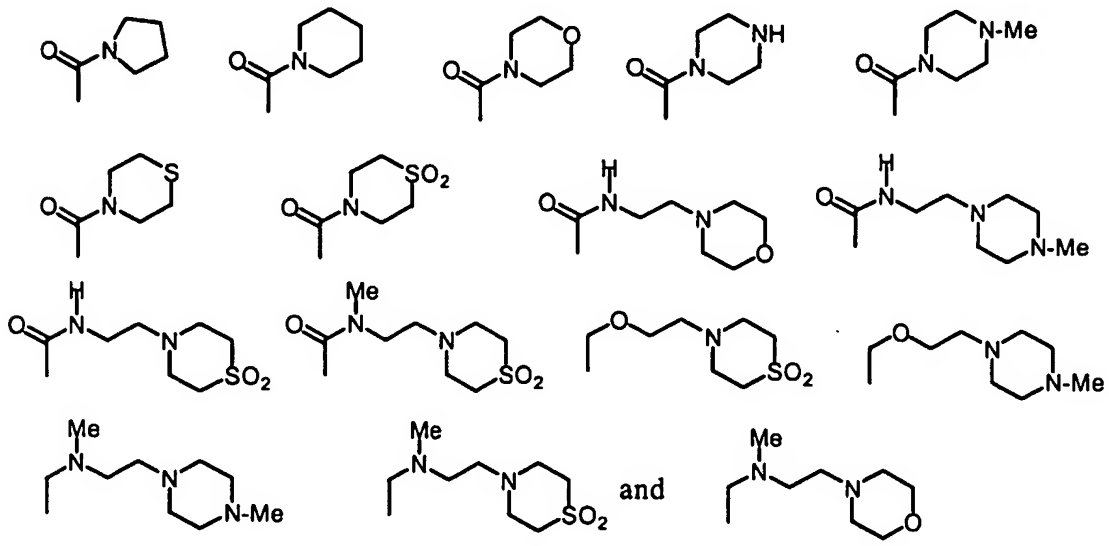
R^6 for each of the above formulae is independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$;

-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

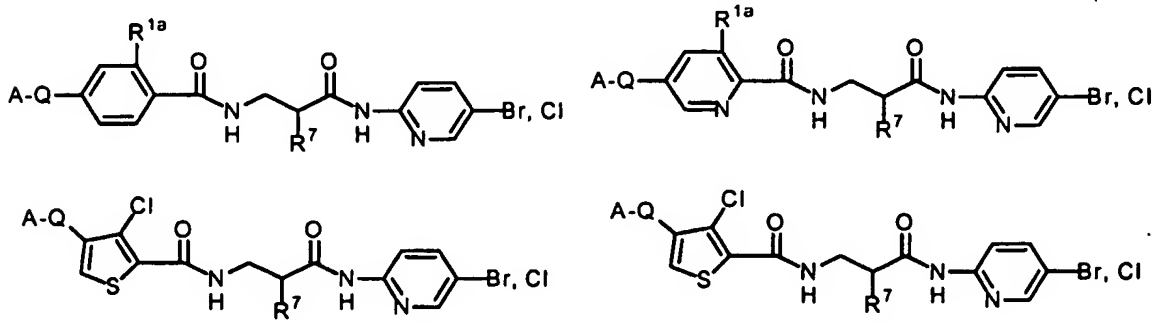
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound having one of the following formulae:



wherein:

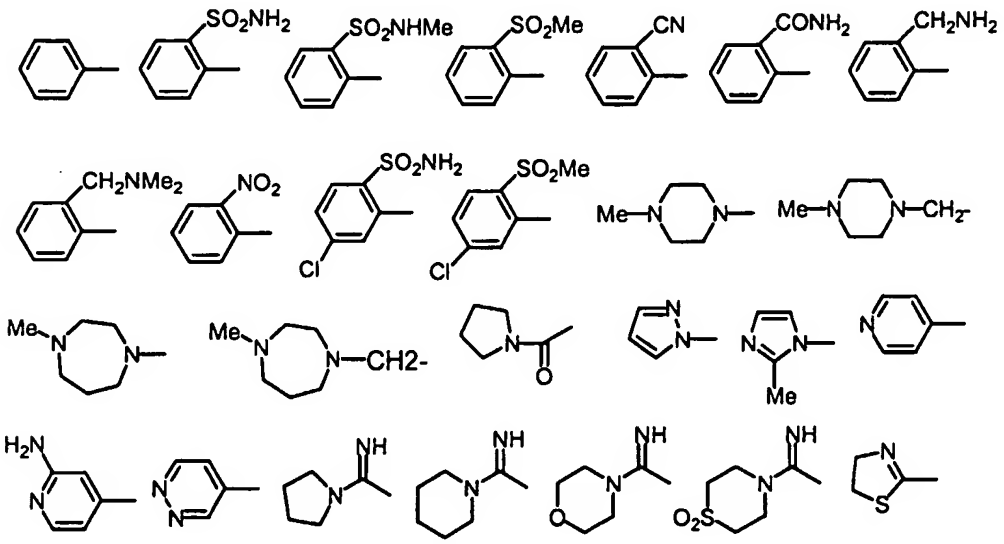
R^{1a}, when it occurs in a formula, is a member selected from the group consisting of:

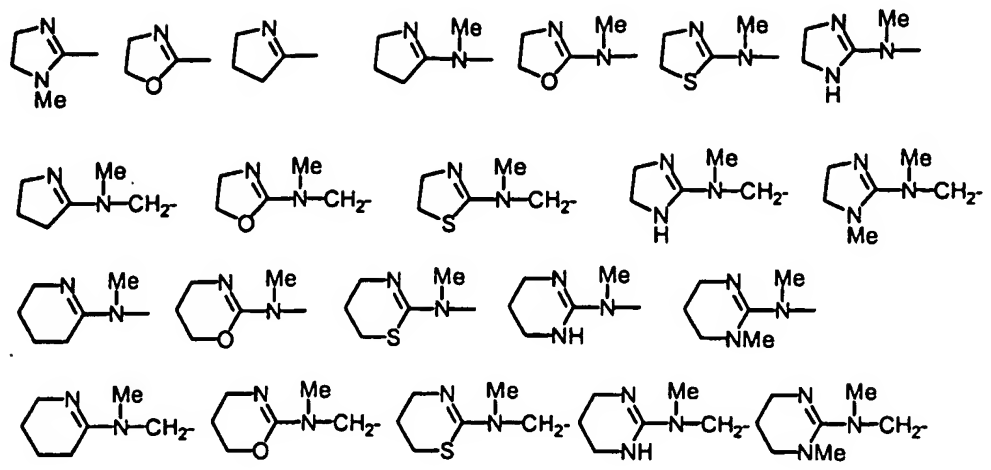
H; -Cl; -F; -Br; -Me; -O-Me; $-NO_2$; -C(=O)-OH; -CN; $-C(=O)-NH_2$ and -C(=O)-O-Me;

R^7 is a member selected from the group consisting of:

H; $-NH_2$; -NH-C(=O)-Me; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; -NH-C(=O)-O-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bu; $-NH-SO_2-Me$; $-NH-SO_2-Me$; $-NH-SO_2-Ph$; $-NH-SO_2-NH-Me$ and $-NH-SO_2-N(-Me)_2$;

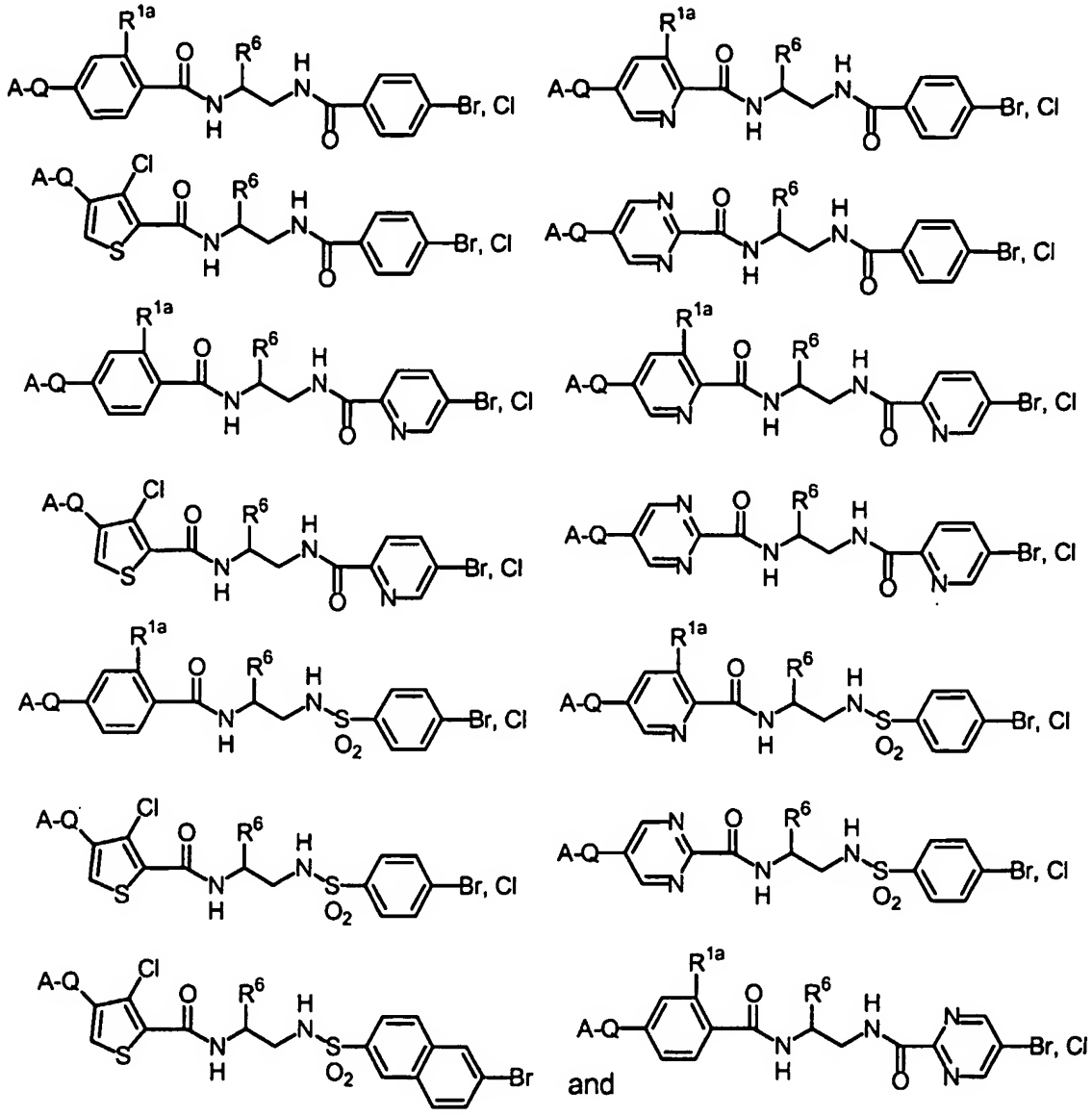
wherein A-Q in each formula is independently a member selected from the group consisting of:





and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment the present invention provides a compound which is a member selected from the following formulae:



wherein:

R^{1a}, when it occurs in a formula, is a member independently selected from the group consisting of:

H; -Cl; -F; -Br; -Me; -O-Me; $-NO_2$; -COOH; -CN, $-C(=O)-NH_2$ and -C(=O)-O-Me;

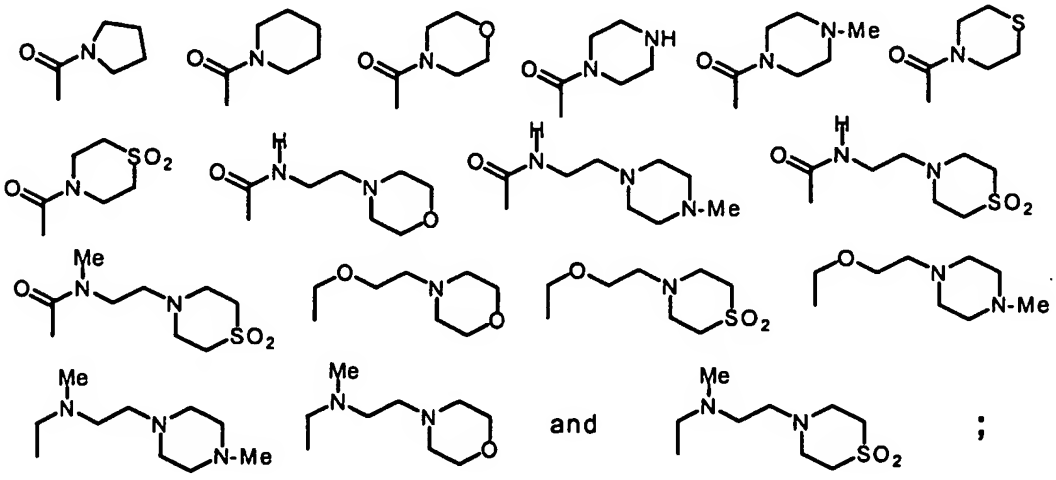
R^6 is independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$;

-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

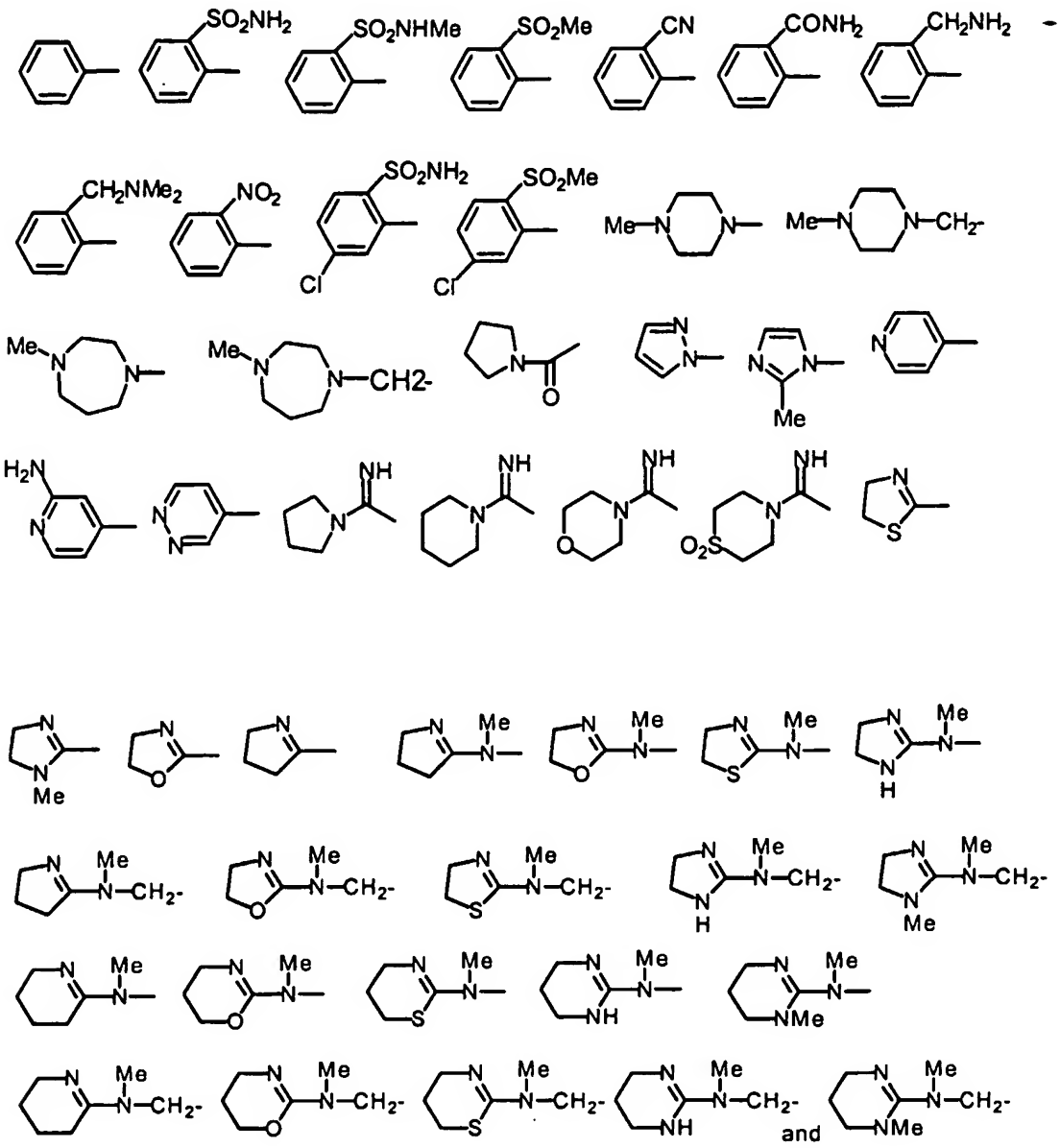
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



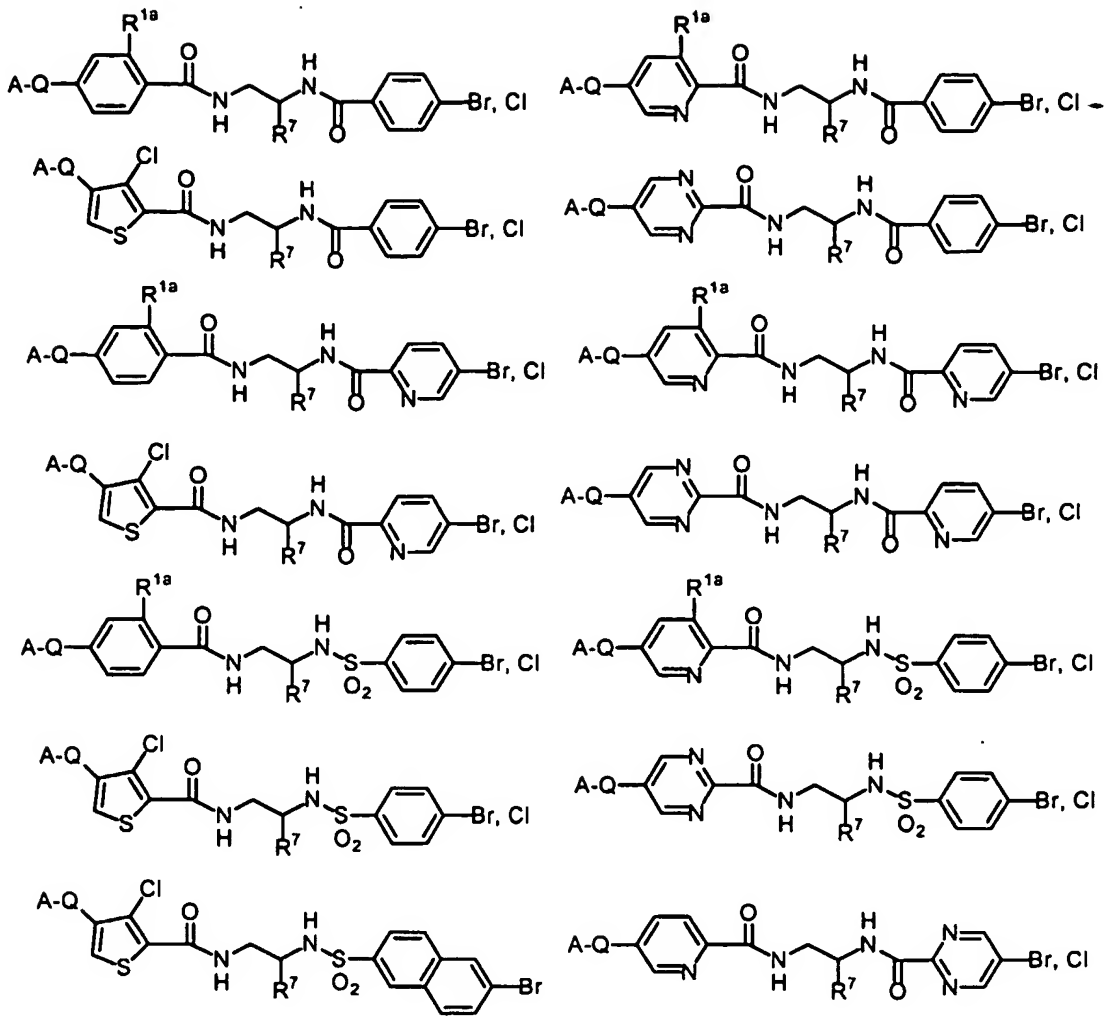
;

A-Q for each of the formulae is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention also provides in one embodiment a compound, which is a member selected from the following formulae:



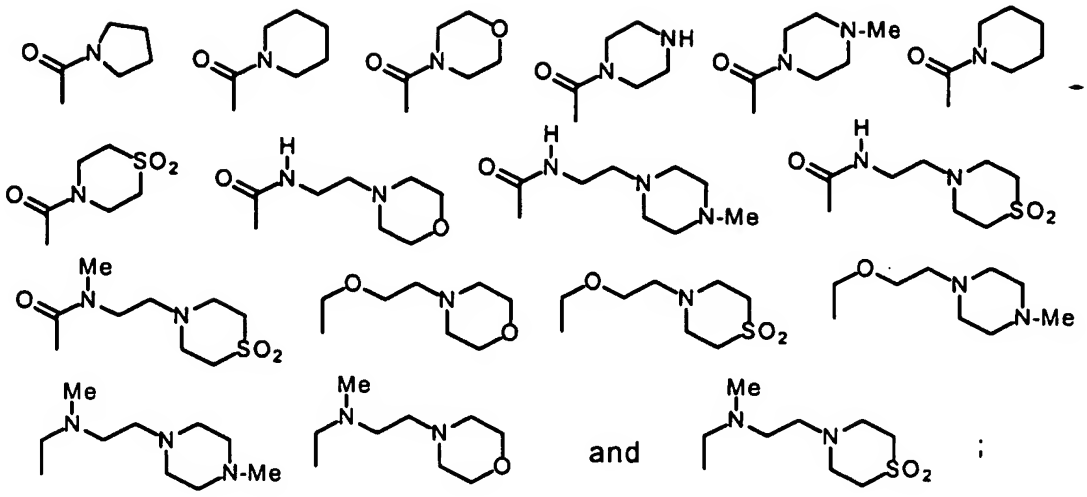
wherein:

R^{1a} is a member selected from the group consisting of:

H; -Cl; -F; -Br; -Me; -O-Me; $-NO_2$; -C(=O)-OH; -CN; $-C(=O)-NH_2$ and -C(=O)-O-Me;

R^7 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$; -COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$; $-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



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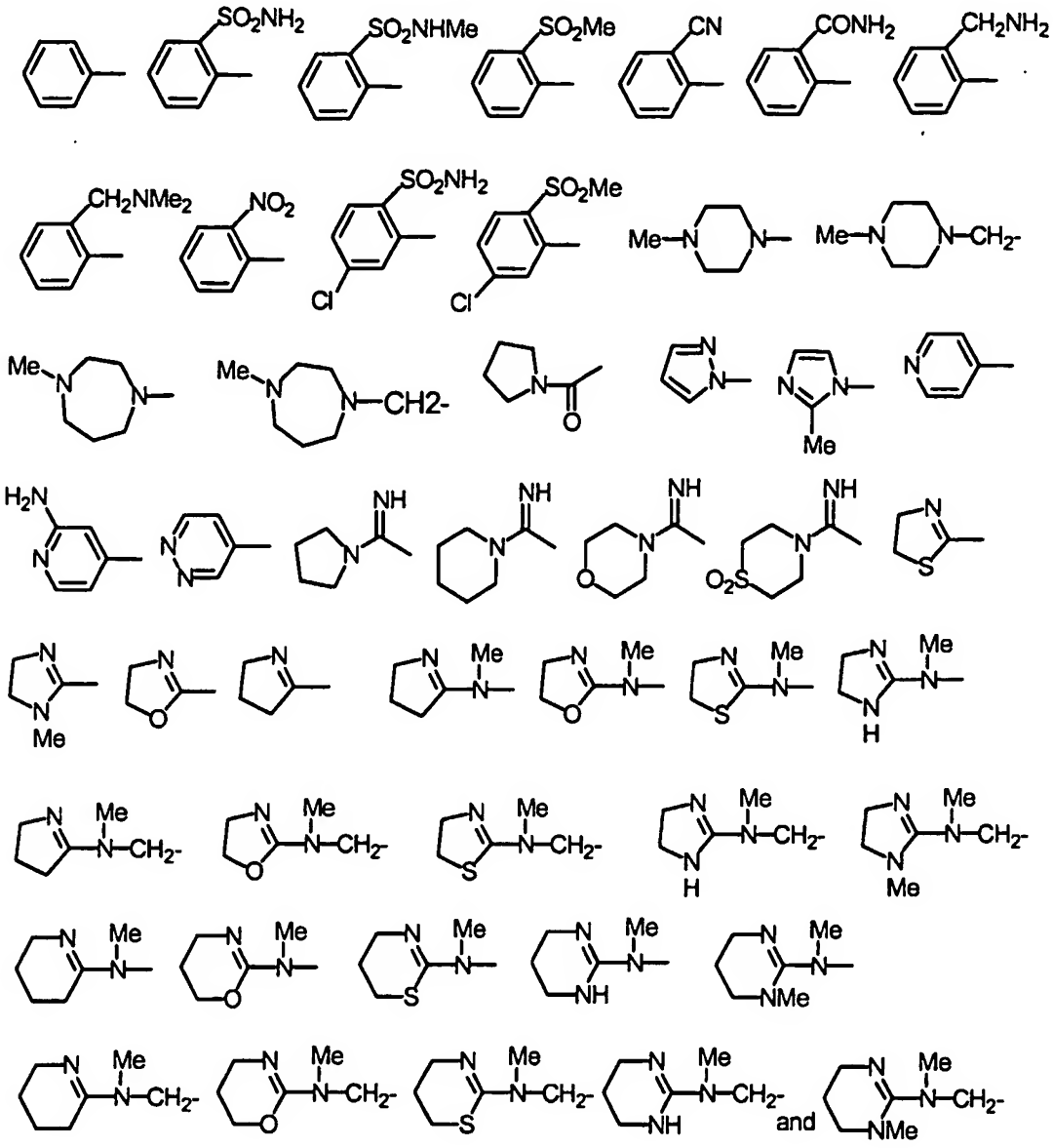
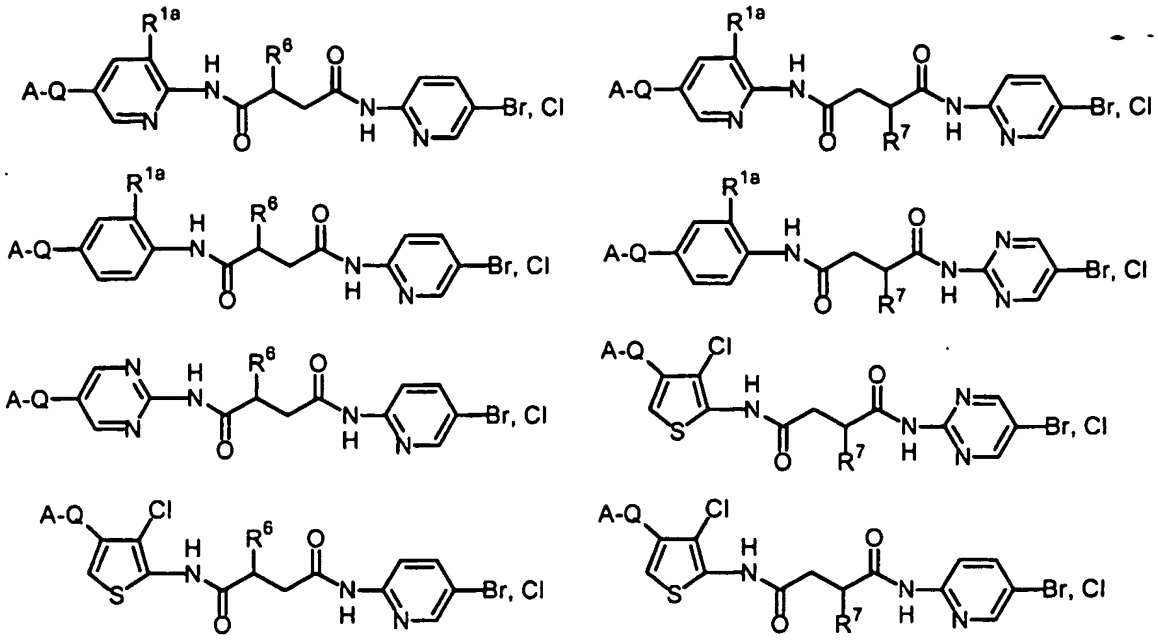
A-Q for each of the formulae is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment, the present invention provides a compound which is a member selected from the following formulae:



wherein

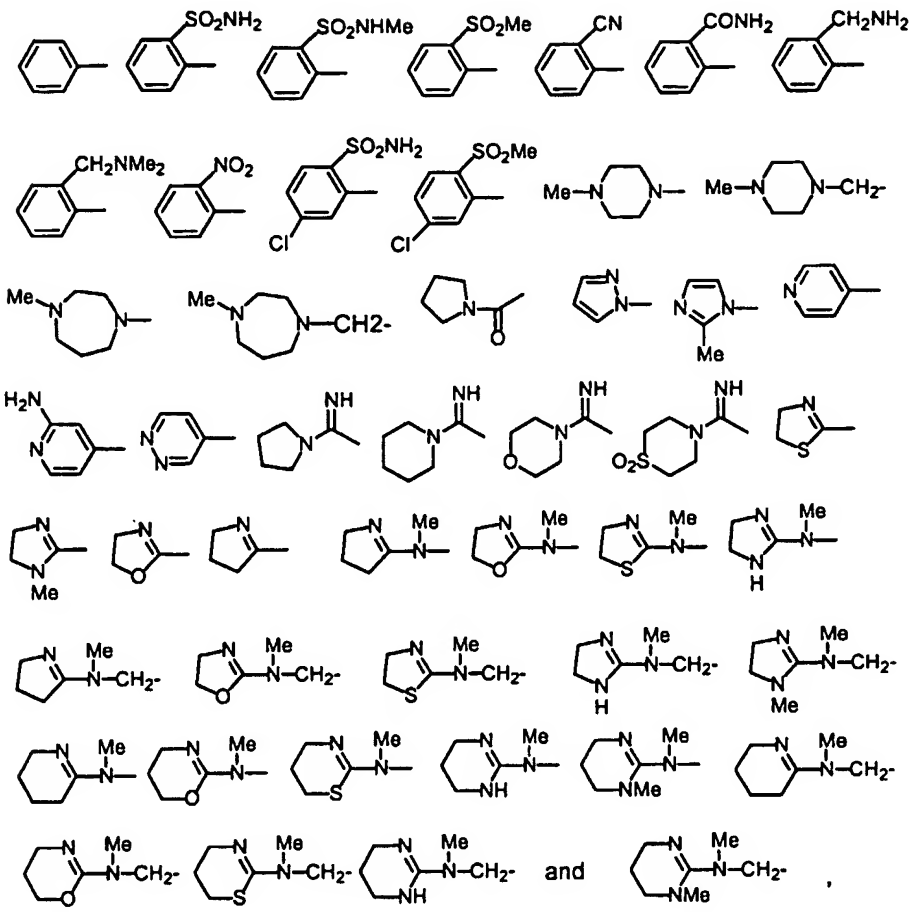
R^{1a}, when the group occurs in a formula, is a member independently selected from the group consisting of:

H, Cl, F, Br, I, NO_2, OMe, Me, COOH, COO-(C_1-C_6 alkyl), $CONH_2$;

R^6 and R^7 are independently selected from:

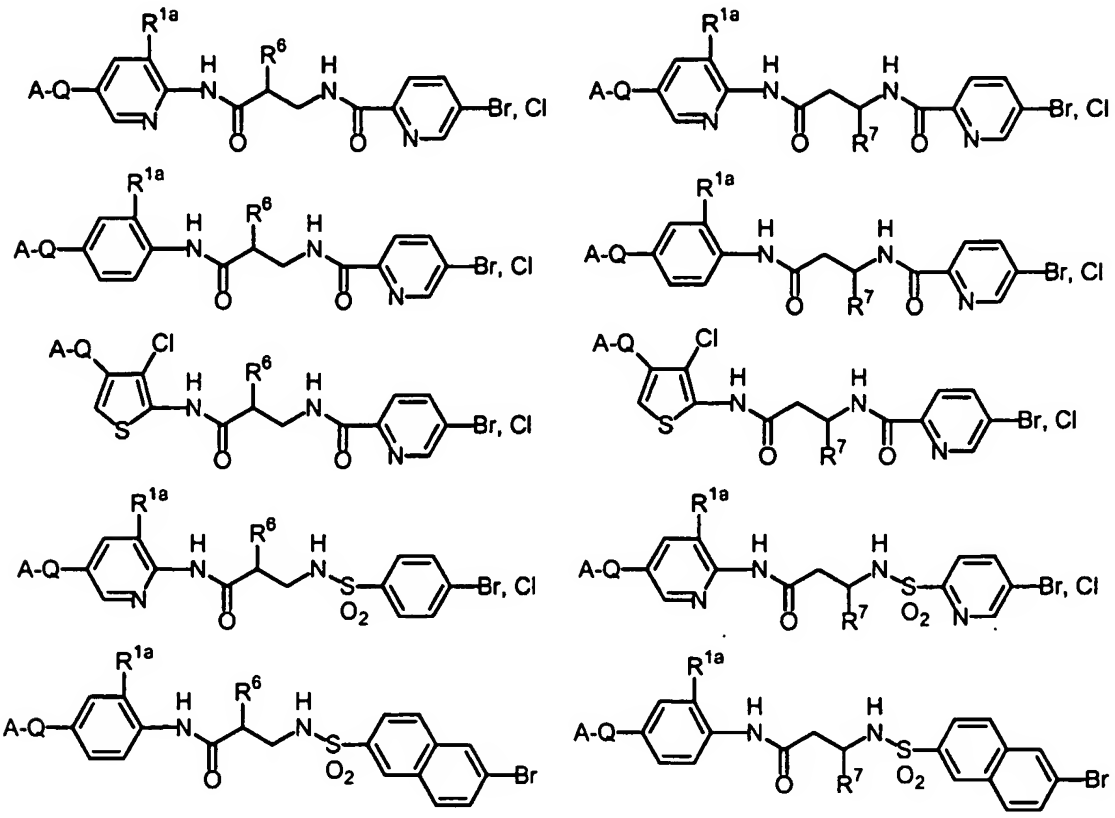
H; -NH_2; -NH-C(=O)-Me; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; -NH-C(=O)-O-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bu; -NH(-SO_2)-Me; -NH-SO_2-Me; -NH-SO_2-Ph; -NH-SO_2-NH-Me and -NH-SO_2-N(-Me)$_2$;

wherein A-Q of each of the above formulae is a member independently selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives thereof.

The invention also provides in one embodiment a compound, which is a member selected from the following formulae:



wherein

R^{1a}, when it is present in a formula, is a member selected from the group consisting of:

H; -Cl; -F; -Br; -I; $-NO_2$; -O-Me; -Me; -C(=O)-OH, -C(=O)-O-(C_1-C_6 alkyl), and -C(-O)-NH_2;

R^6, when it is present in a formula, is a member selected from the group consisting of:

H; $-NH_2$; -NH-C(=O)-Me; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; -NH-C(=O)-O-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bu; -NH($-SO_2$)-Me; -NH-SO_2-Me; -NH-SO_2-Ph; -NH-SO_2-NH-Me and -NH-SO_2-N(-Me)$_2$;

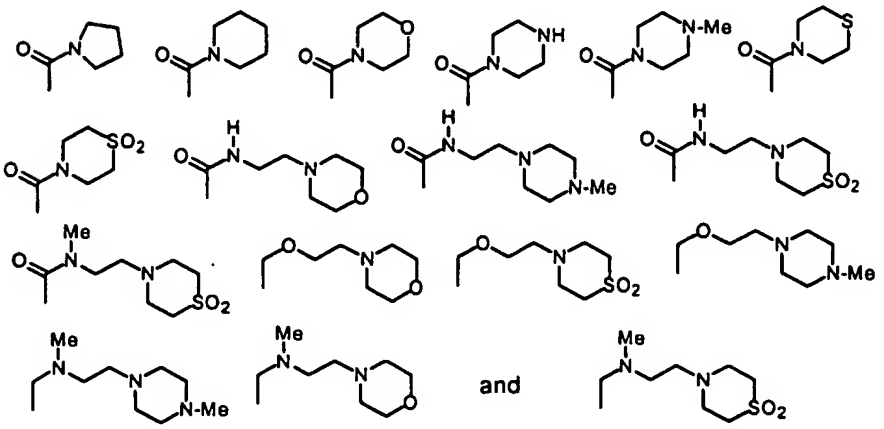
R^7, when it is present in a formula, is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$;

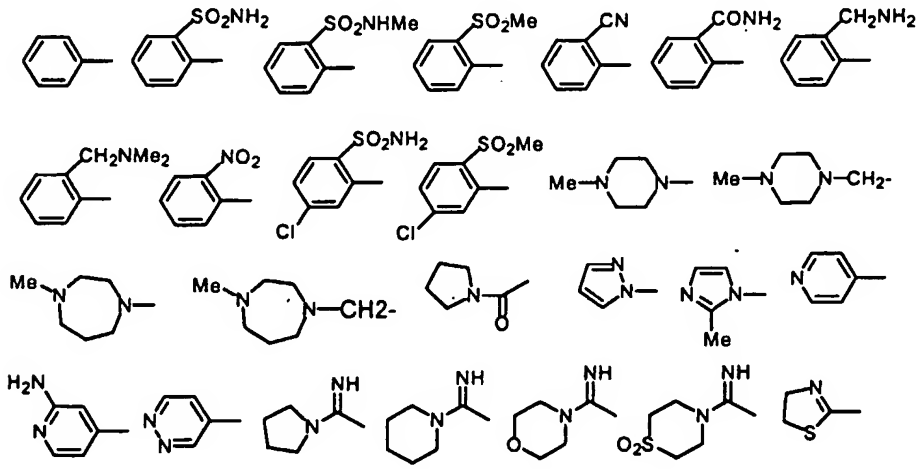
-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

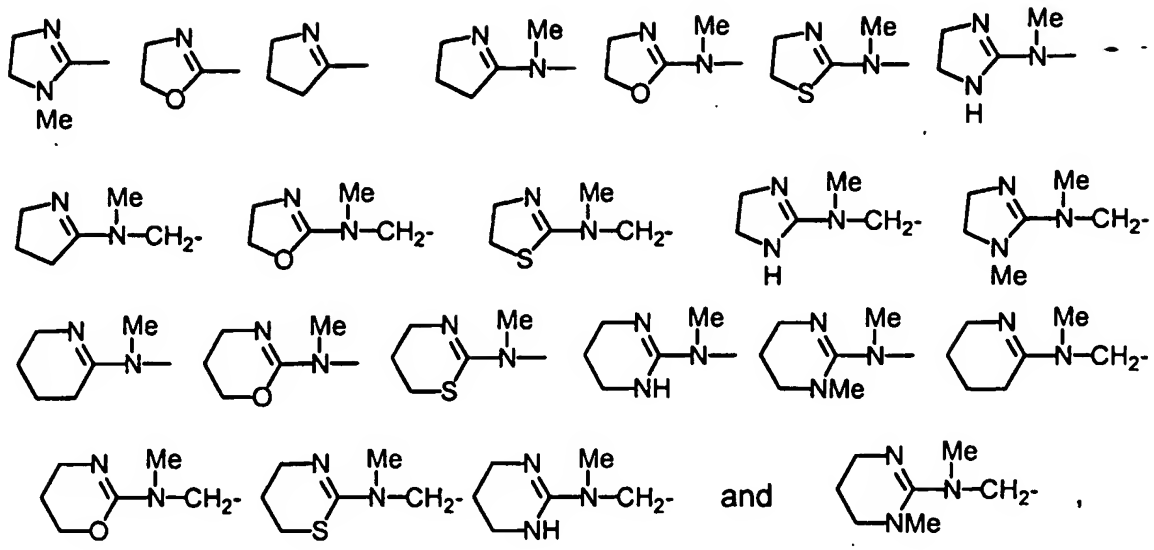
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



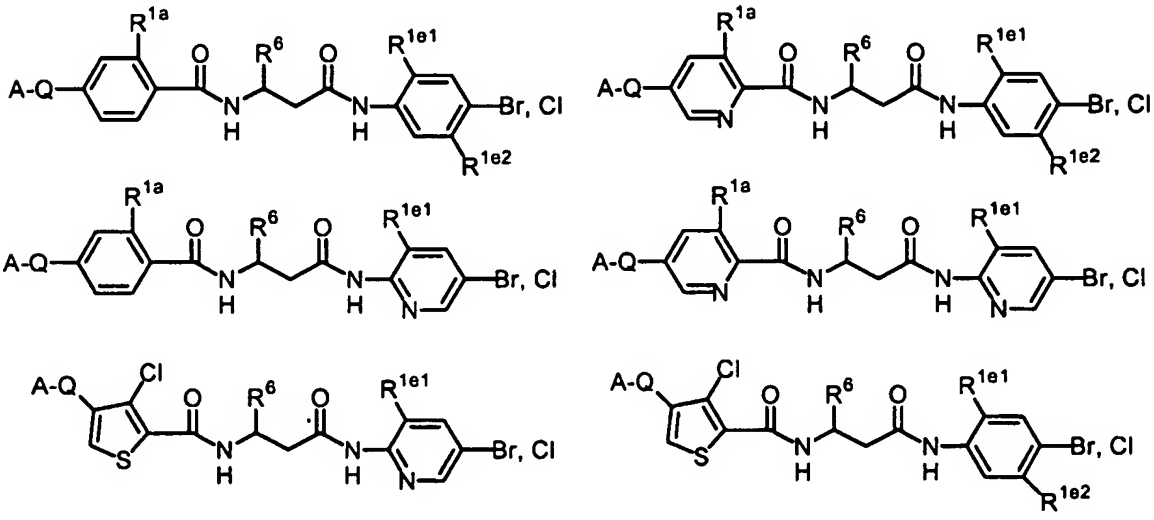
A-Q is selected from:





and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment, the present invention provides a compound which is a member selected from the following formulae where X is substituted with 0-3 R^{1c} as illustrated:



wherein:

R^{1a}, when present, is a member independently selected from the group consisting of:

H; -Cl; -F; -Br; $-NO_2$; -O-Me; -C(=O)-OH; -C(=O)-OEt and $-C(=O)-NH_2$;

R^{1e1}, when present, is a member independently selected from the group consisting of:

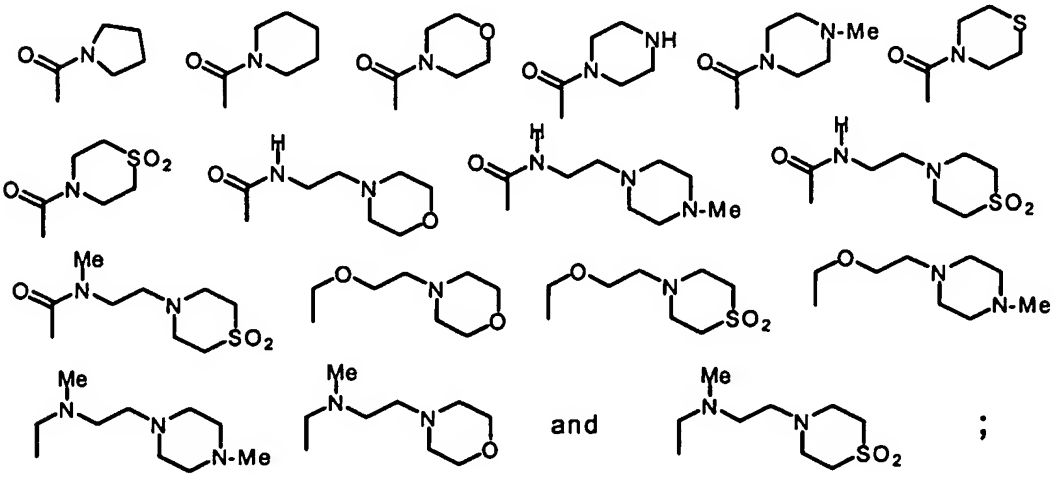
H; -Cl; -Br; -OH; $-NO_2$; -O-Me; $-NH_2$; $-CH_2-NH_2$; -NH-Me; $-CH_2-OH$; $-CH_2-O-Me$; -CN; $-C(=O)-NH_2$; -C(=O)-NH-Me; $-SO_2-Me$; $-SO_2-NH_2$ and $-SO_2-NH-Me$;

R^{1e2}, when present, is a member independently selected from the group consisting of:

H; -Me; -O-Me; -Cl; -Fl; -Br; $-CF_3$; $-C(=O)-NH_2$; -CN; -C(=O)-OH; $-C(=O)-O-Me$; $-SO_2-Me$; $-SO_2-NH_2$; $-SO_2-NH-Me$ and $-NO_2$;

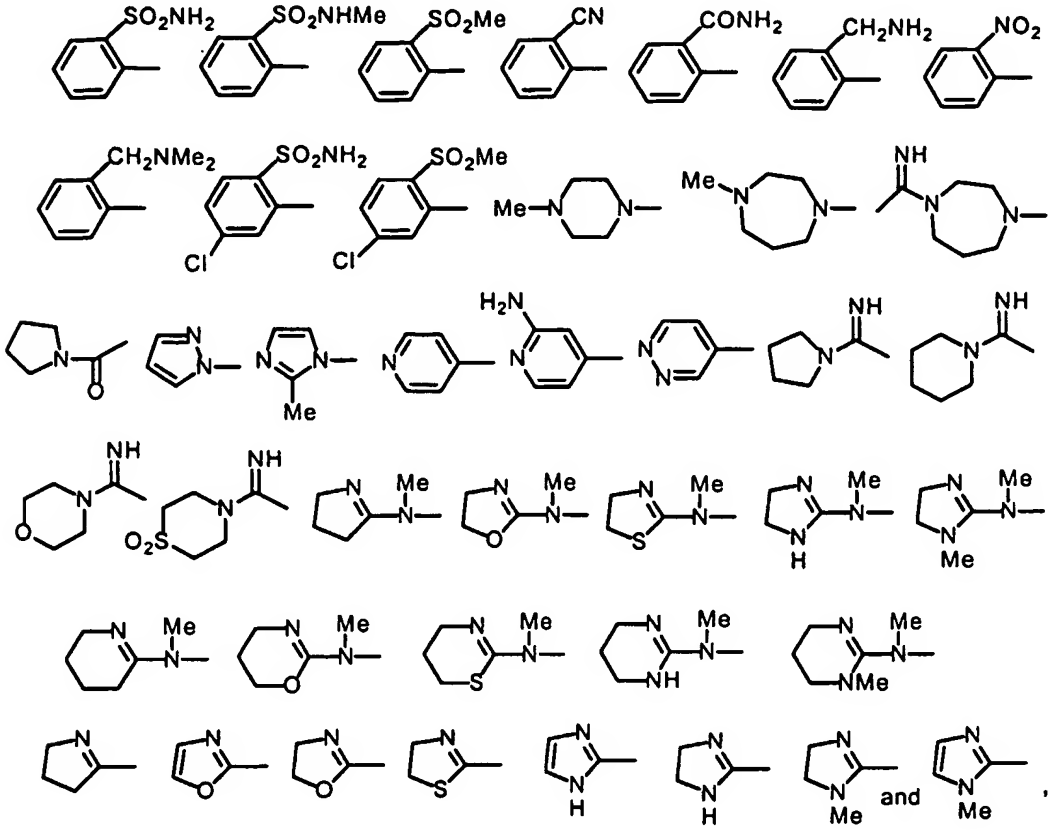
R^6 is independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$; -COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$; $-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



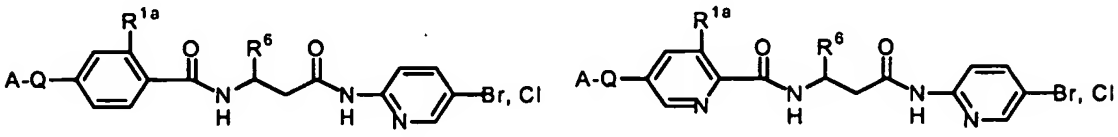
;

A-Q for each of the above formula, is independently a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Most preferably, the present invention provides a compound which is a member selected from the group consisting of the following formulae:



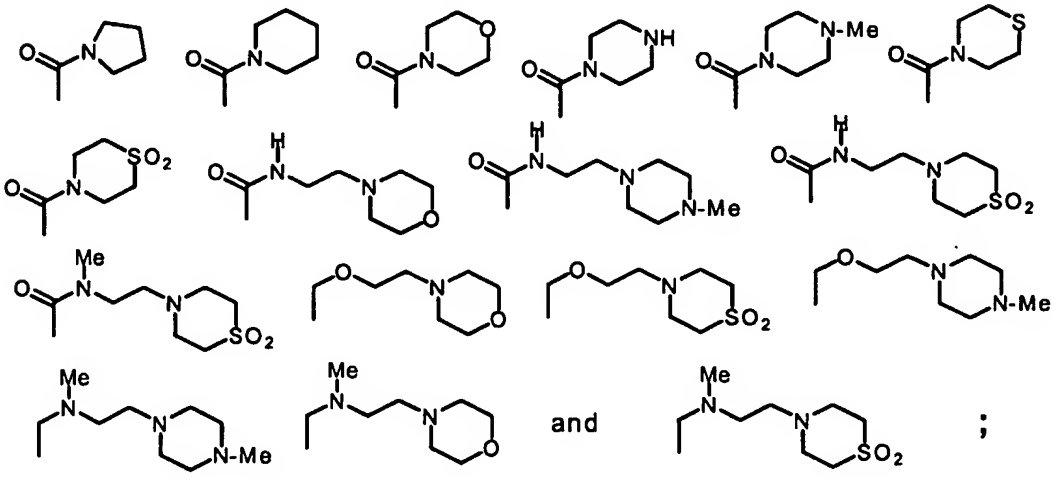
wherein:

R^{1a} is independently a member selected from the group consisting of:

H; -Cl; -F; -Br; -Me; $-NO_2$; -O-Me; -C(=O)-OH; -C(=O)-O-Me and $-C(=O)-NH_2$;

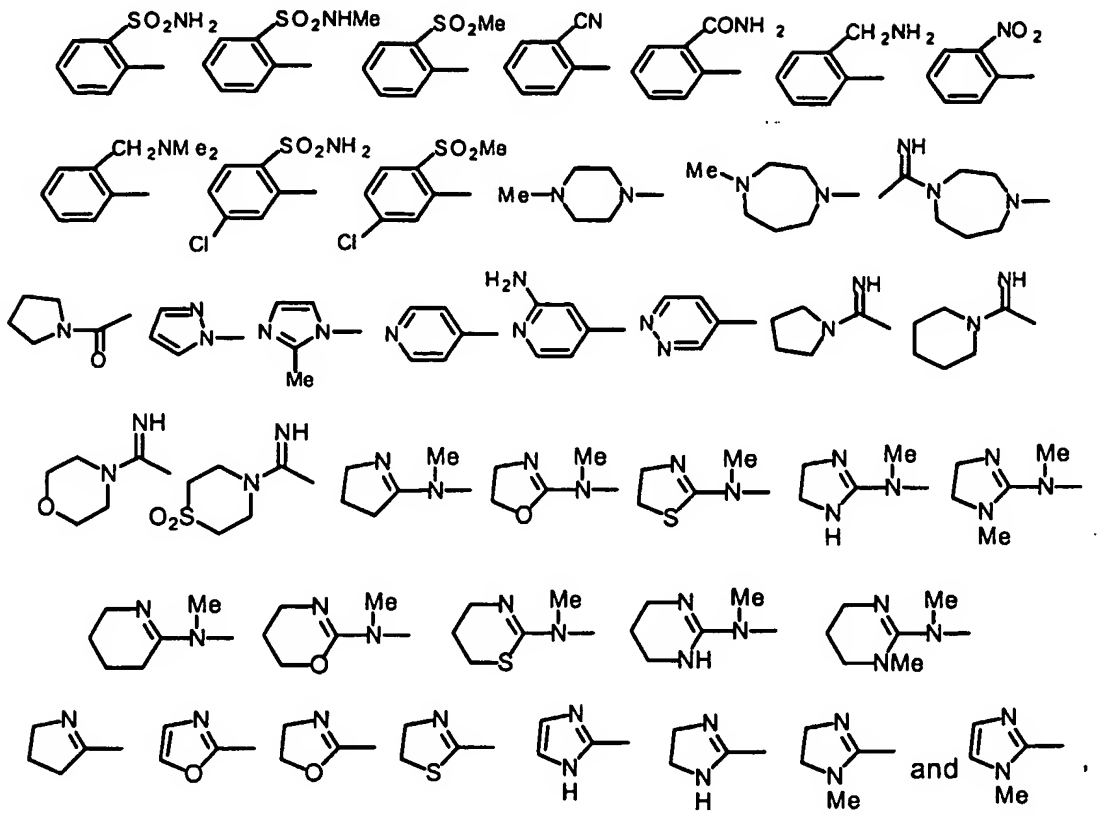
R^6 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2)_2-COOH$; -COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$; $-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



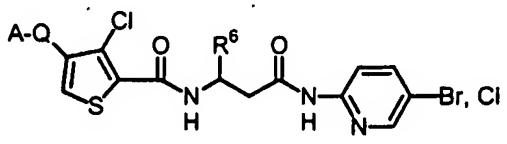
;

A-Q is a member selected from the group consisting of:



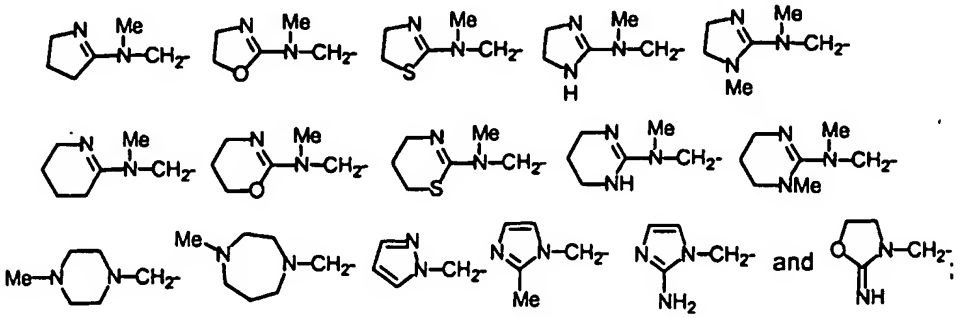
and all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives thereof.

Even more preferred, the present invention provides a compound of the following formula:



wherein

A-Q is a member independently selected from the group consisting of:



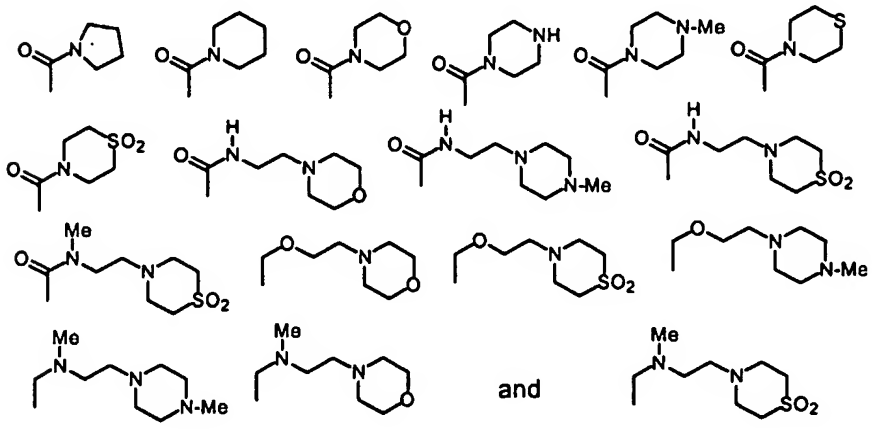
R^6 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2)_2-COOH$;

-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Even further preferred, the present invention provides compounds according to the following formulae of Table 1:

Table 1

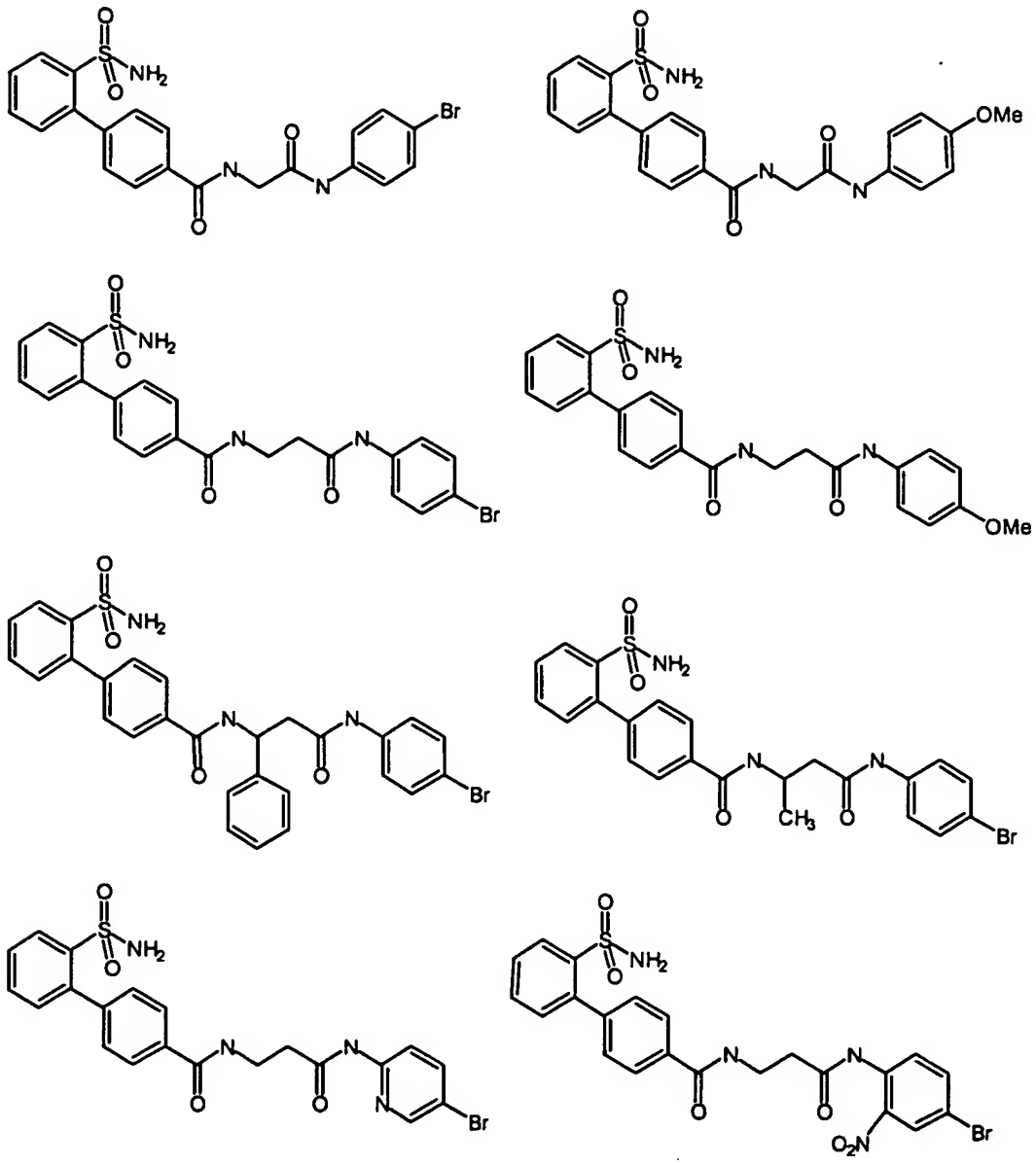
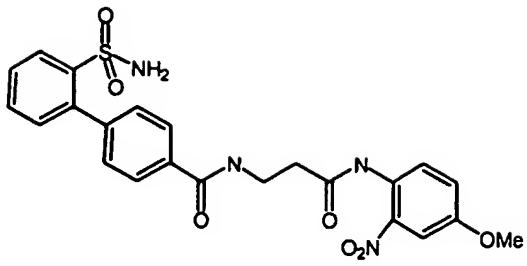
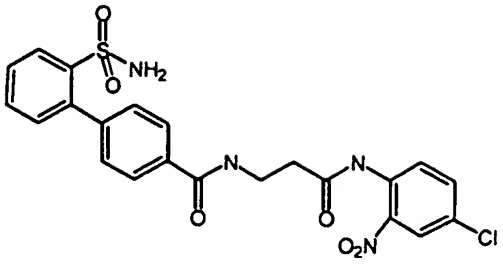
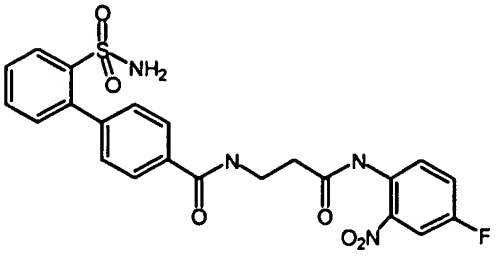
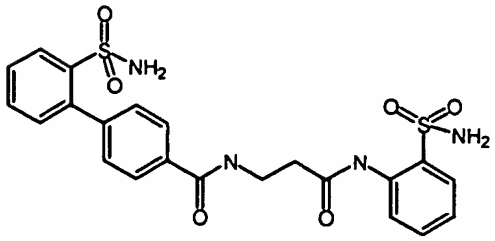


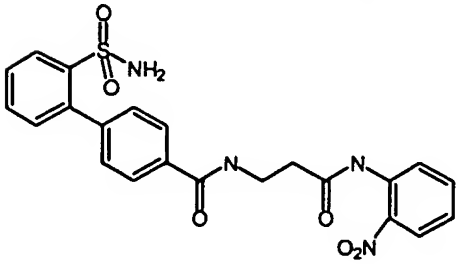
Table 1 (Cont.)

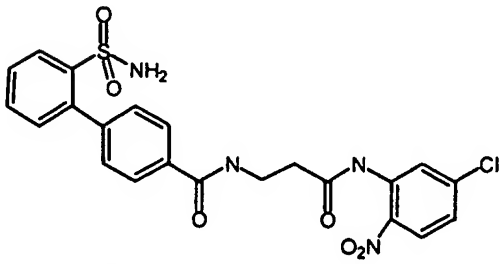


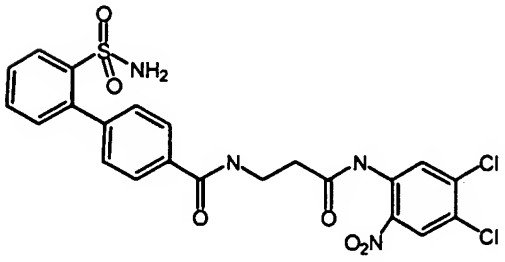


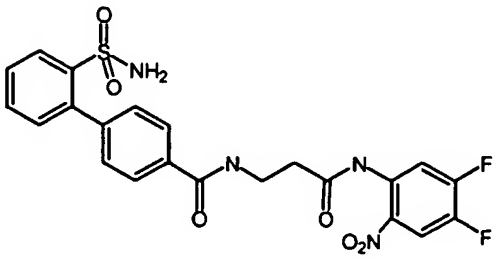


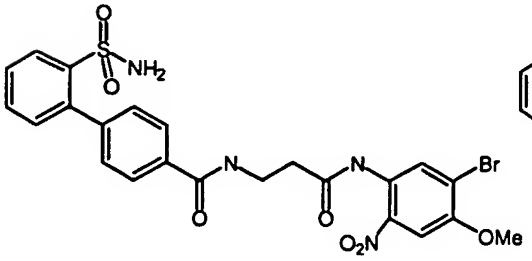












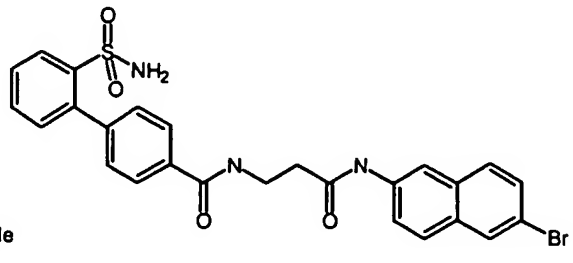
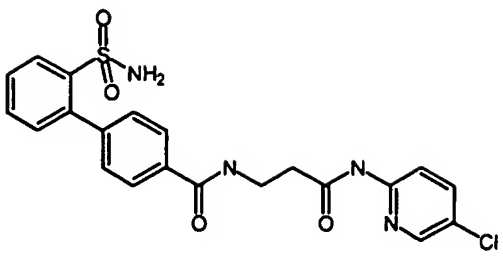
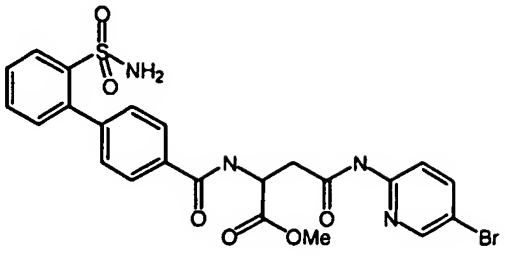
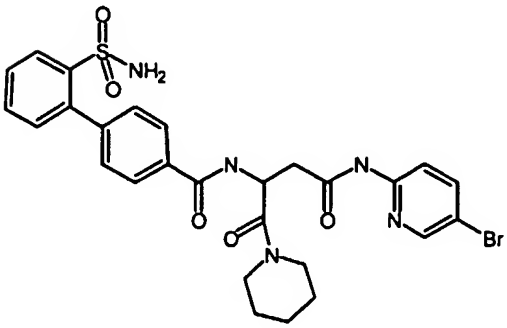
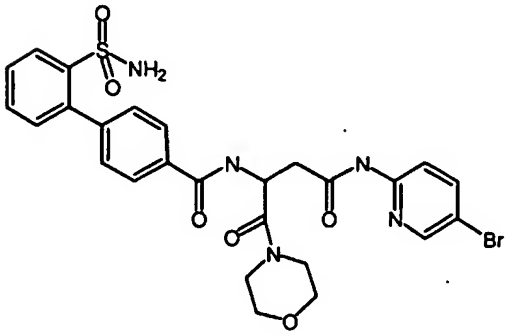


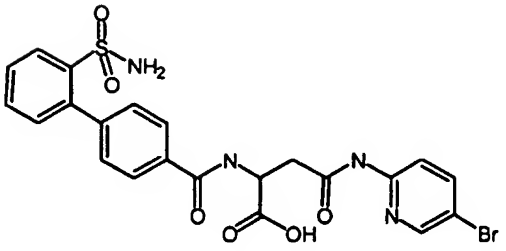
Table 1 (Cont.)

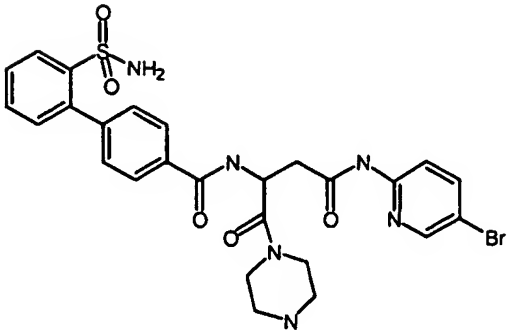


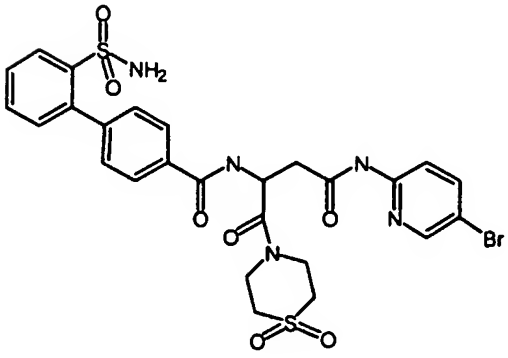


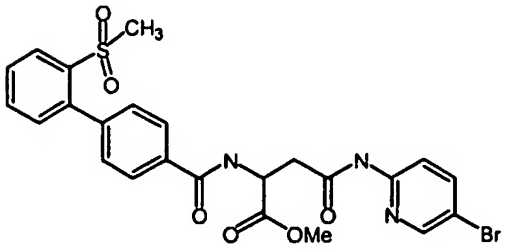












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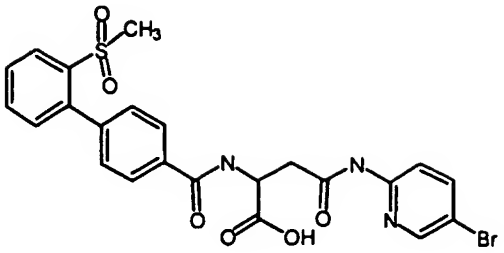

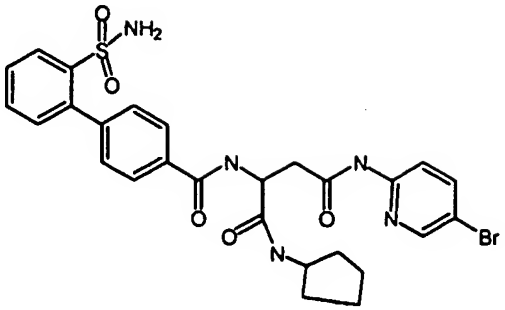

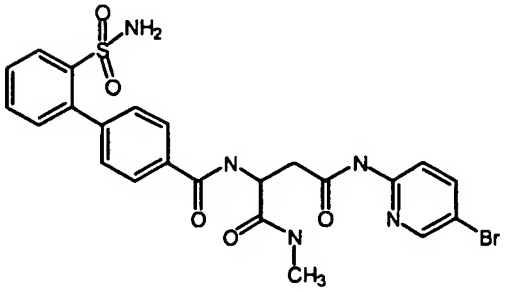

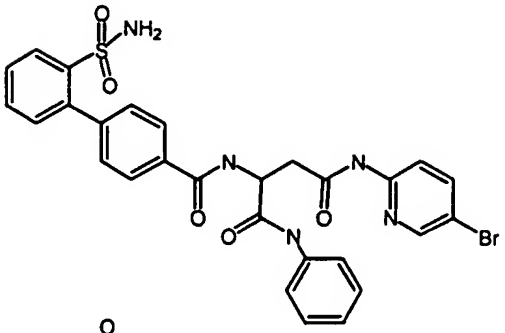

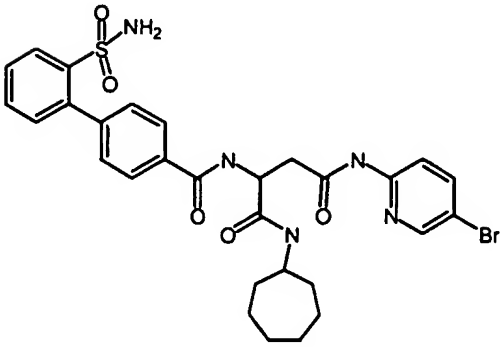

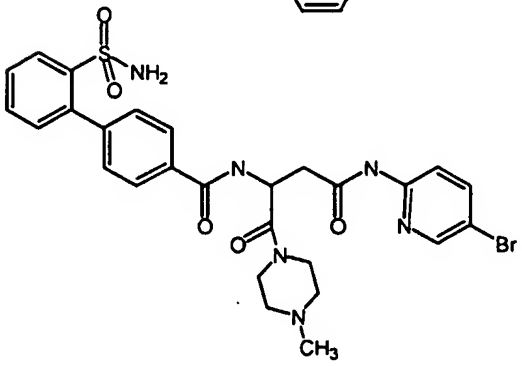

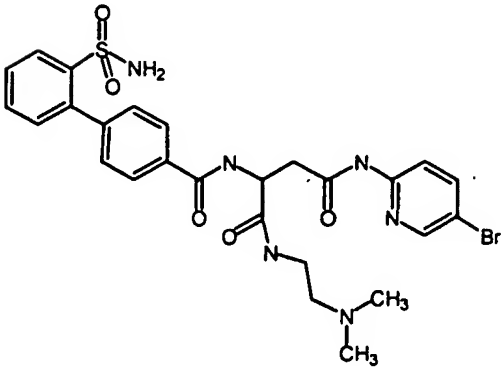

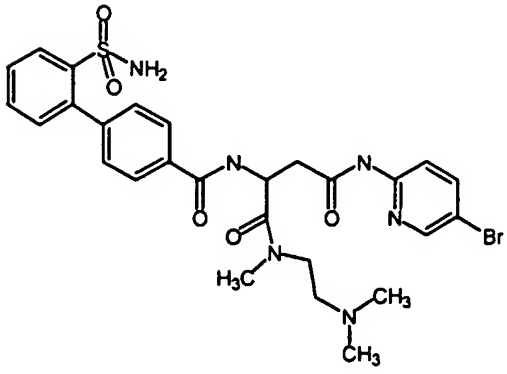

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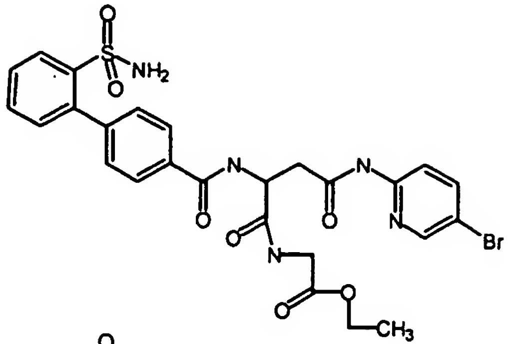
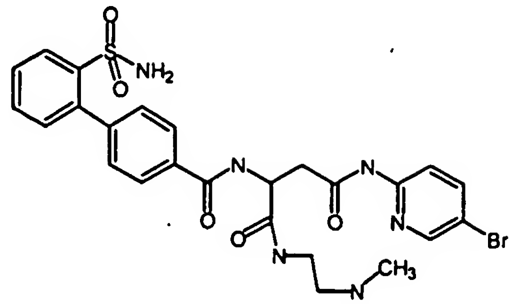
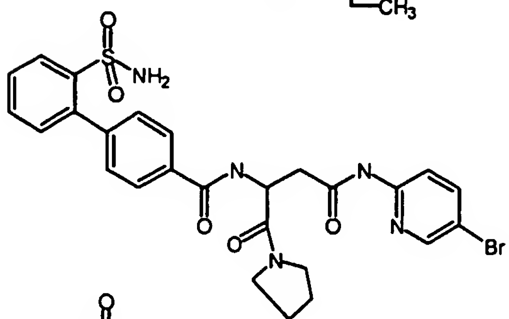
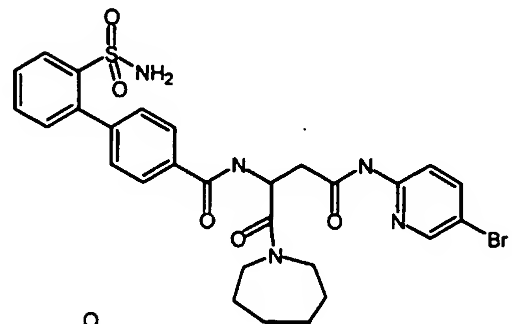
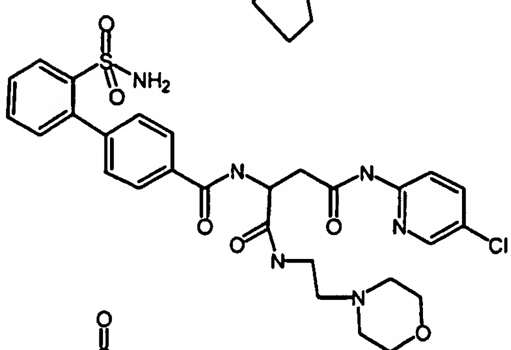
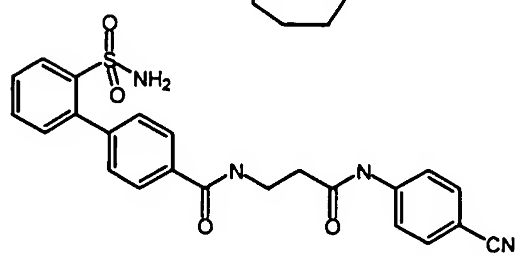


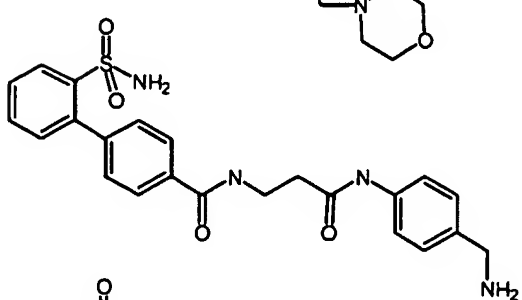


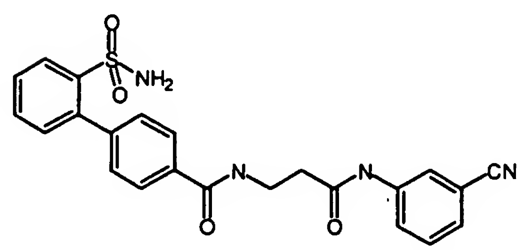


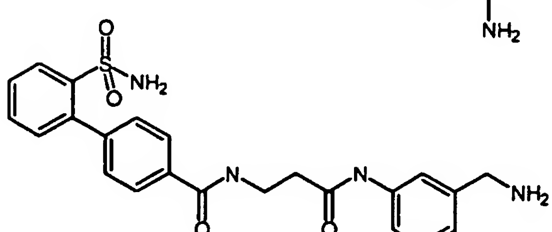












This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives of the compounds of the above formulae. In addition, the compounds of such formulae can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on

the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or

percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration,

suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the

formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the

physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by standard organic chemical synthetic methods as described and referenced in standard textbooks. These methods are well known in the art. See, e.g., Morrison and Boyd, "Organic Chemistry", Allyn and Bacon, Inc., Boston, 1959, et seq.

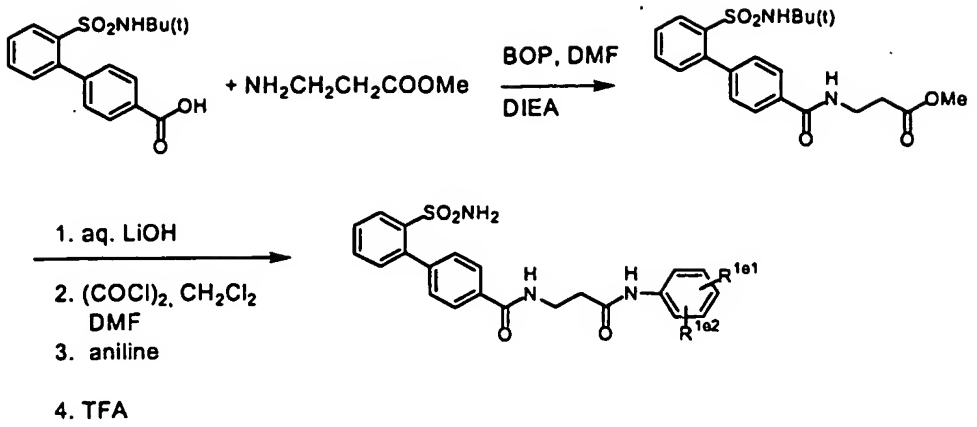
Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

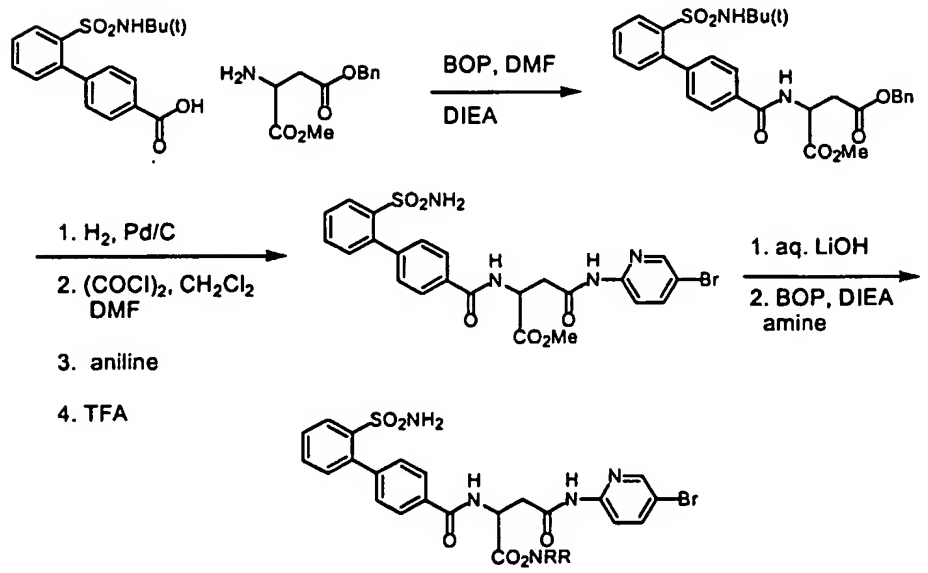
During the synthesis of these compounds, the functional groups of the substituents are optionally protected by blocking groups to prevent cross reaction during coupling procedures. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Non-limiting exemplary synthesis schemes are outlined directly below, and specific steps are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Scheme 1



Scheme 2



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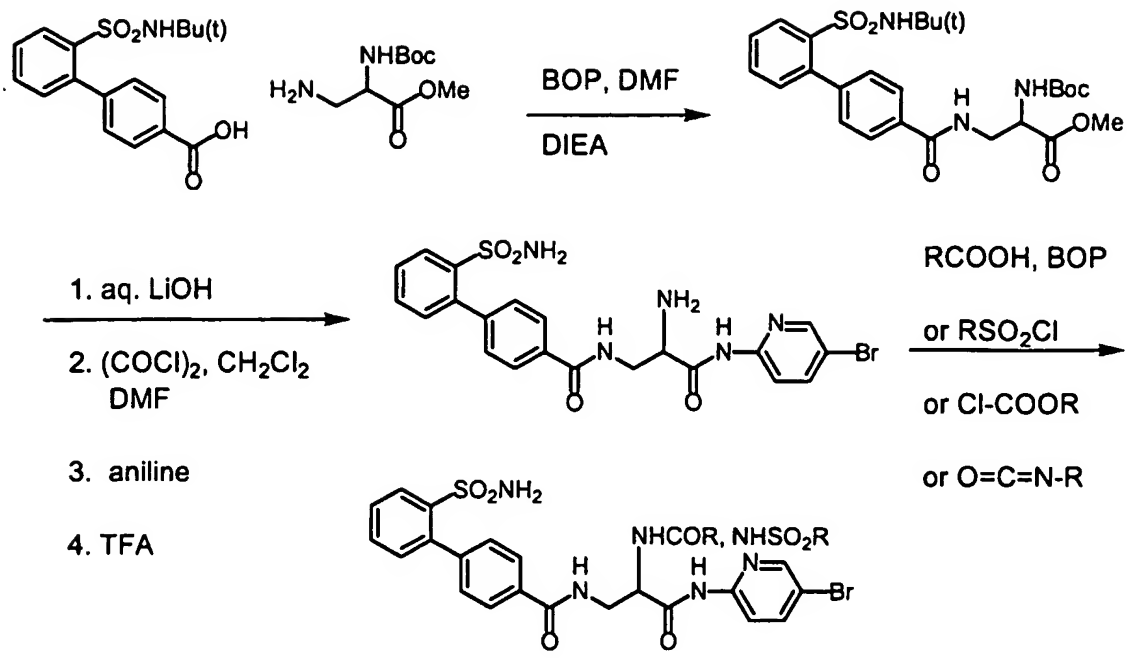

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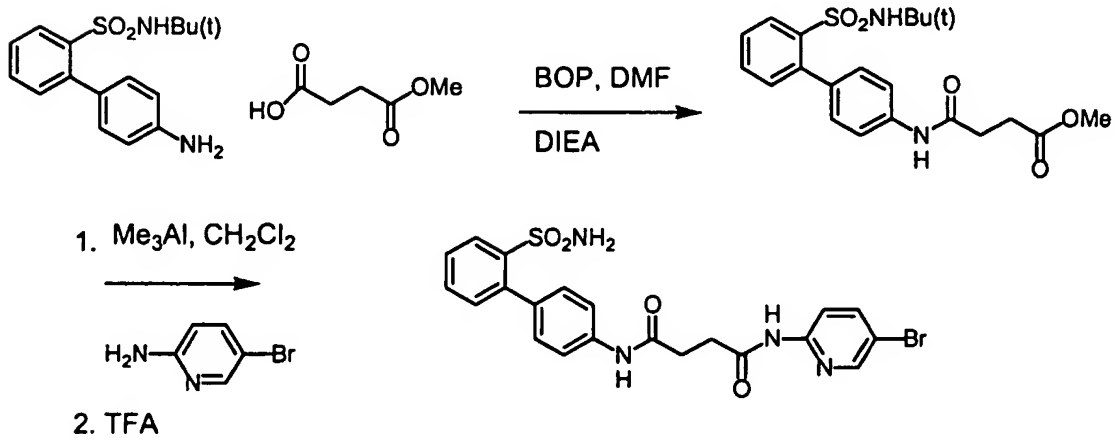

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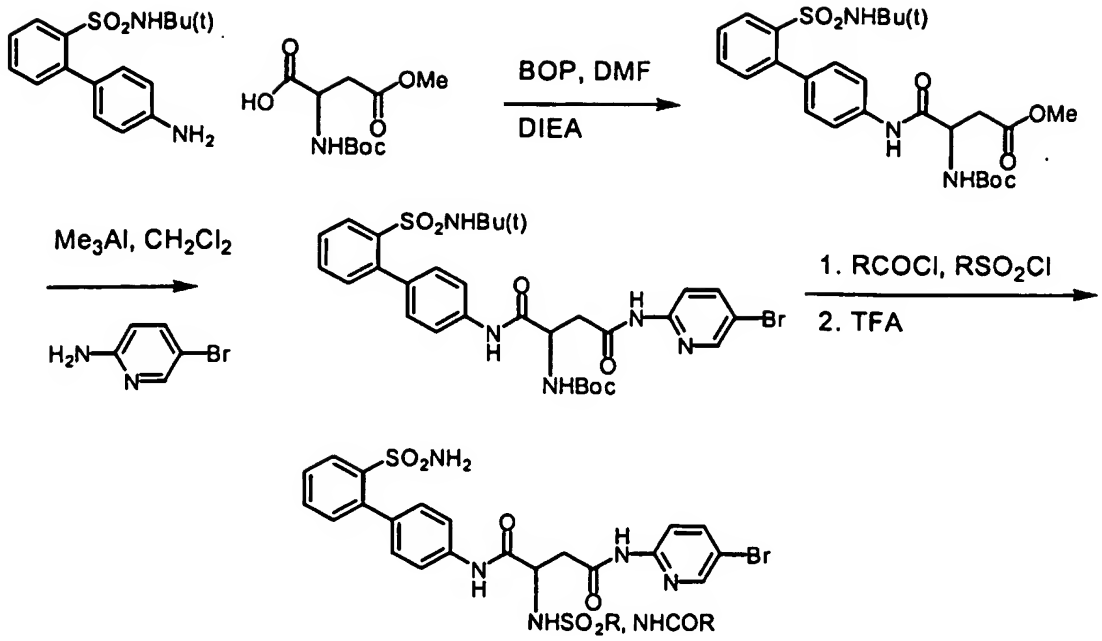
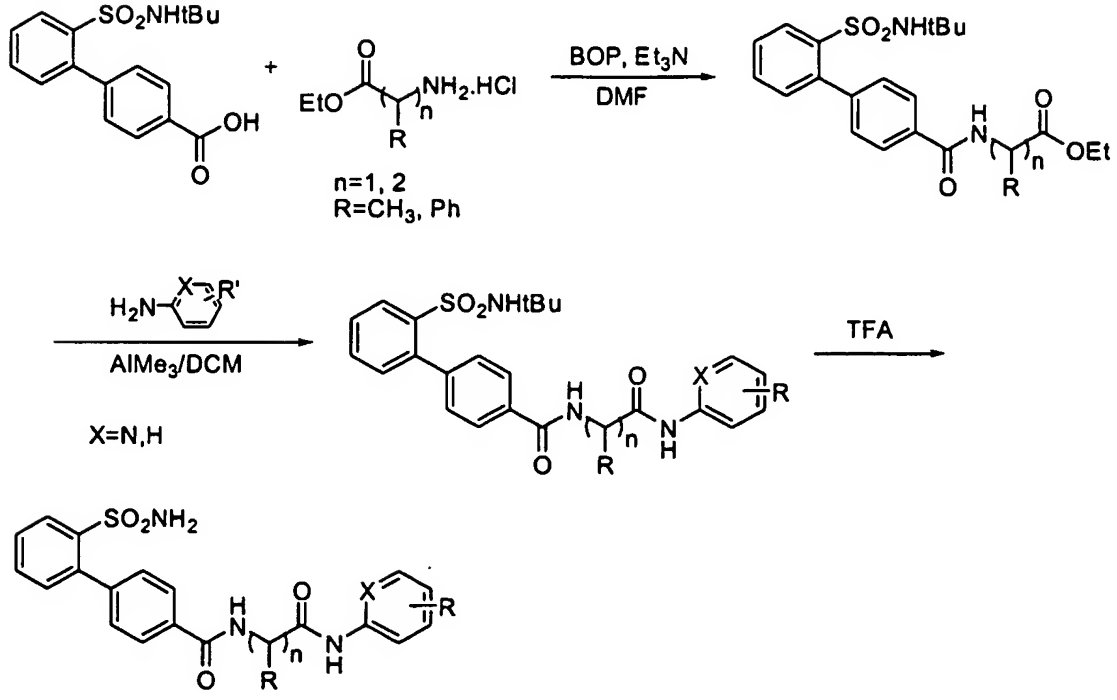
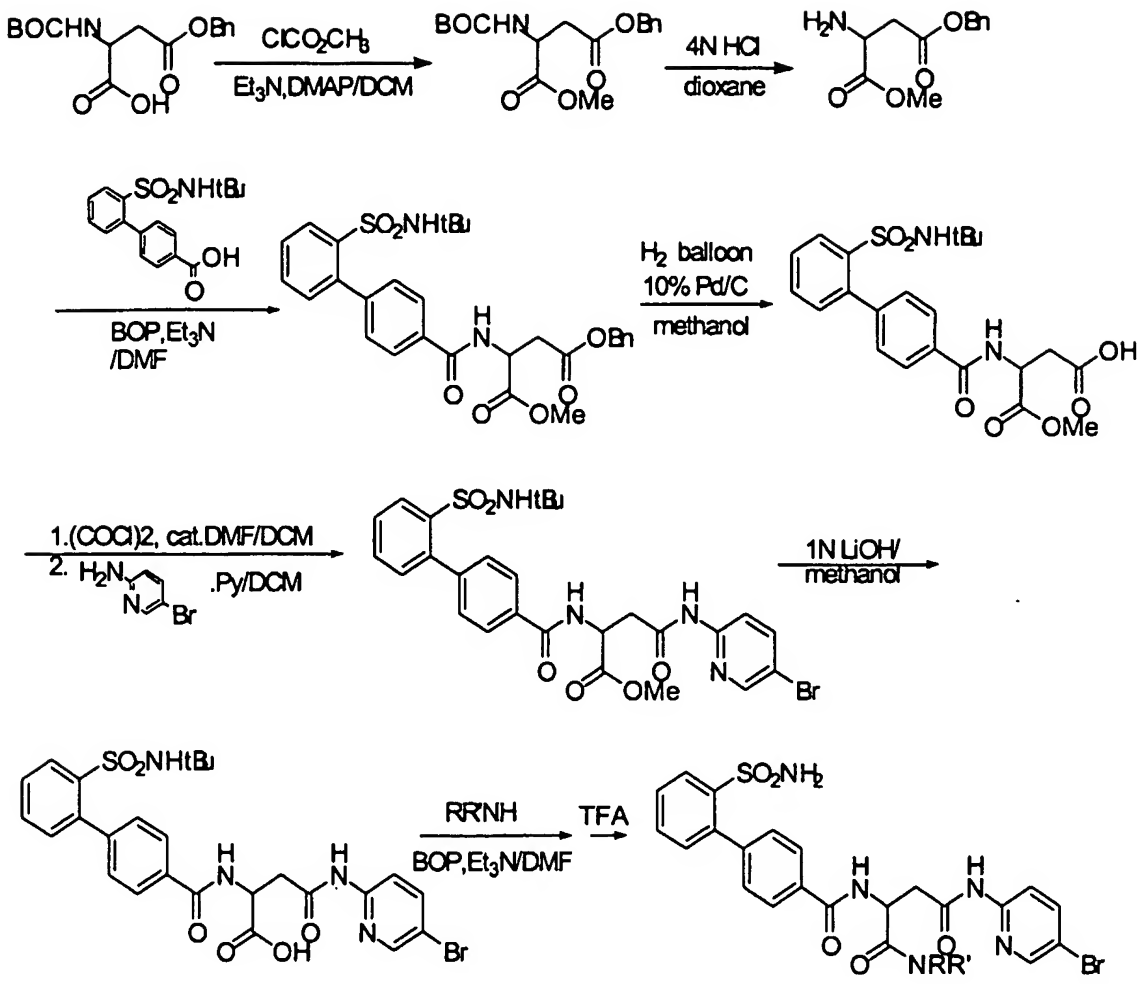
Scheme 5



Scheme 6



Scheme 7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OMe
4N HCl
dioxane
H2N
SO2NHtBu
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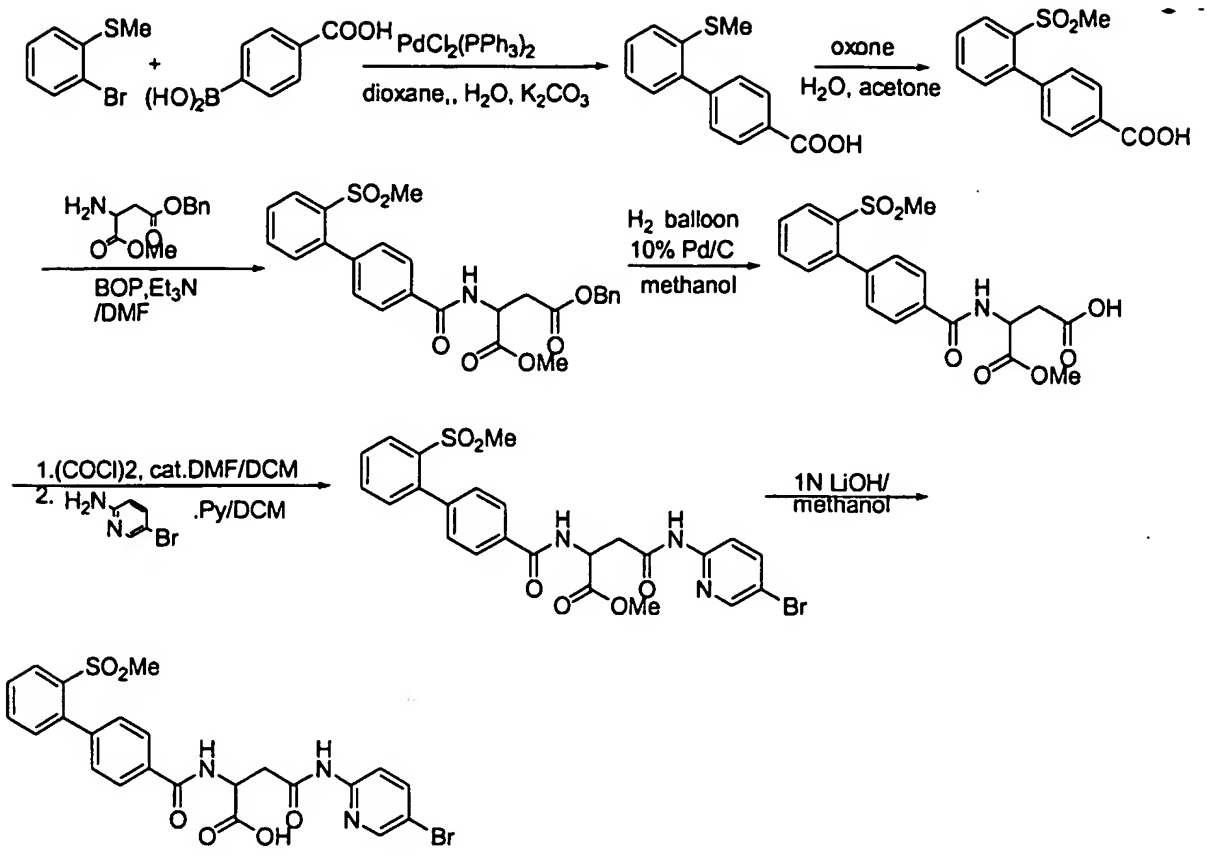
/DMF
H2 balloon
10% Pd/C
methanol
1.(COCl)2, cat.DMF/DCM
2. H2N
Br
.Py/DCM
1N LiOH/
methanol
RR'NH
TFA
BOP,Et3N/DMF
SO2NH2
NRR'

Scheme 8



Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or

base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon

caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical

practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications

associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

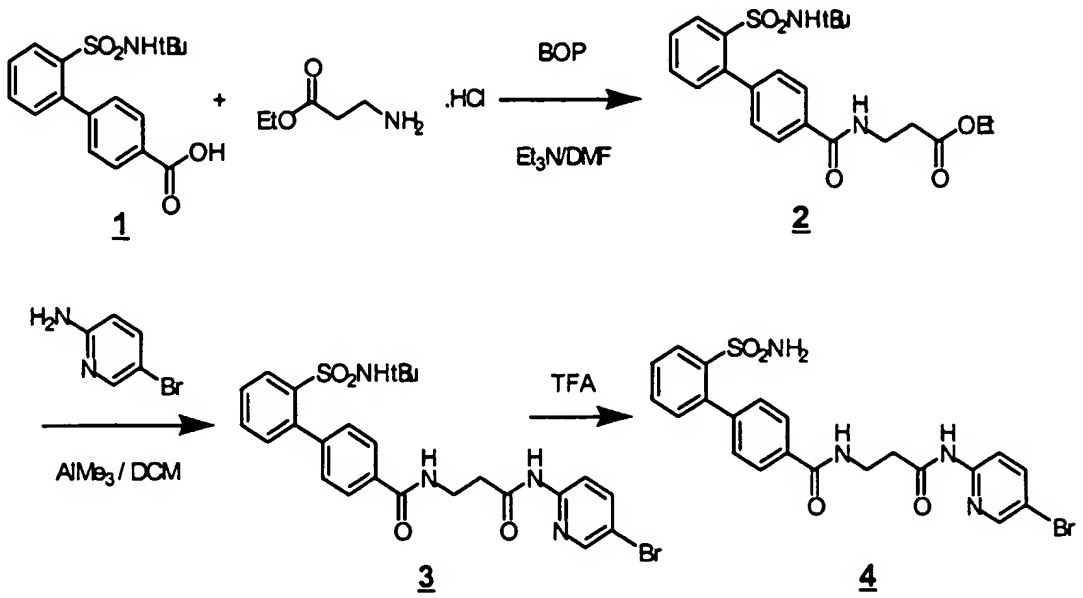
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

Example 1

The synthesis of Example 1 is accomplished according to the following scheme.



To a solution of 1(1.12g, 3.4mmol) in DMF (10 mL) were added β-alanine ethyl ester hydrochloride (0.62g, 4mmol), BOP (1.79g, 4mmol) and TEA (0.94ml, 6.7mmol). The solution was stirred at room temperature overnight. After the removal of the solvent, the crude product was purified by flash column (40%-50% ethyl acetate in hexane) to give 1.46g (100% yield) of 2.

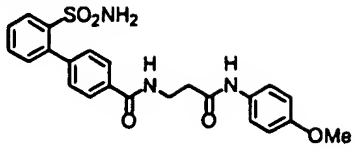
To a solution of 2-amino-5-bromopyridine (64mg, 0.37mmol) in DCM (2ml) was added 2.0M trimethylaluminum in hexane (0.56ml, 1.11mmol). The mixture was stirred at room temperature for 30 minutes and methane gas was evolved. A solution of 2(160mg, 0.37mmol) in DCM (1ml) was added. The mixture was stirred at room temperature overnight. 1N aq. HCl was added to acidify the solution to pH = 2. After the addition of H_2O and DCM, the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over $Mg2SO_4$ and concentrated *in vacuo* to give 30mg (15%) of 3.

30mg (0.05mmol) of 3 was treated with neat TFA (2ml). The mixture was stirred at room temperature for 3 hrs. After the removal of TFA, the crude product was purified by preparative HPLC to give 22mg (78%) of 4. ES-MS $[M+H]^+$ m/z = 503.0 and 505.0.

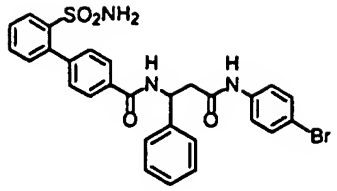
5

The following Examples 2-23 were synthesized using the general procedures described in examples and by following the procedures shown above for reaction Schemes 1-8:

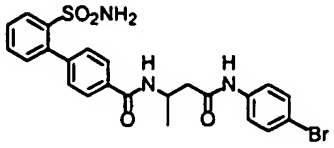
Examples 2-23:



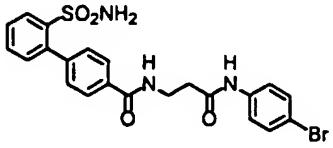
ES-MS $[M+H]^+$ m/z = 454.10



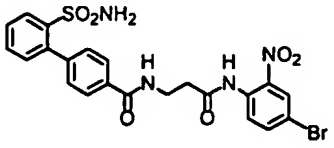
ES-MS $[M+H]^+$ m/z = 578.0 and 580.2



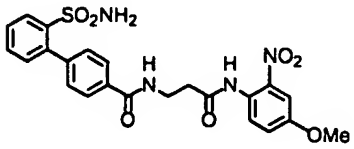
ES-MS $[M+H]^+$ m/z = 516.05 and 518.05



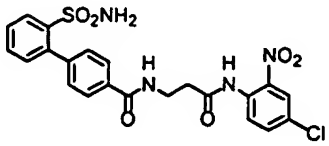
ES-MS $[M+H]^+$ m/z = 502.0 and 504.0



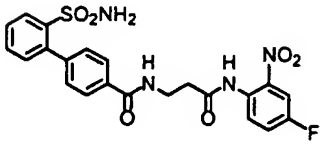
ES-MS $[M+H]^+$ m/z = 547.0 and 549.0



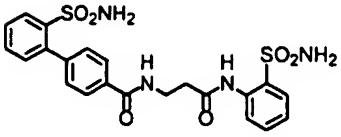
ES-MS $[M+H]^+$ m/z = 499.10



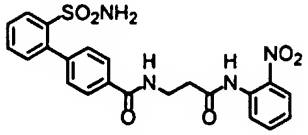
ES-MS $[M+H]^+$ m/z = 503.05



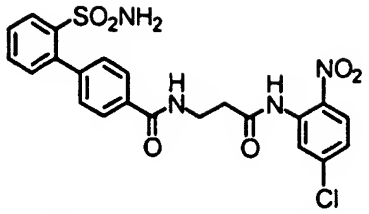
ES-MS $[M+H]^+$ m/z = 487.05



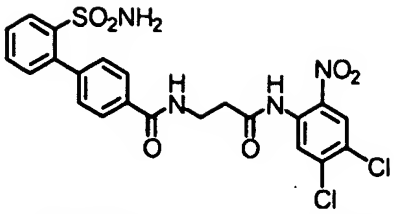
ES-MS $[M+H]^+$ m/z = 503.10



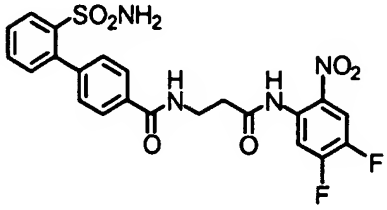
ES-MS $[M+H]^+$ m/z = 469.10



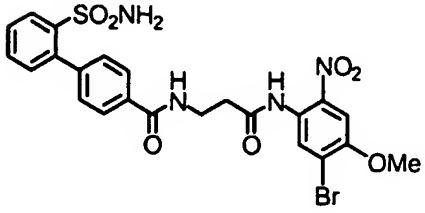
ES-MS $[M+H]^+$ m/z = 503.05



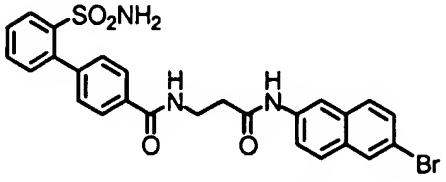
ES-MS $[M+H]^+$ m/z = 538.95



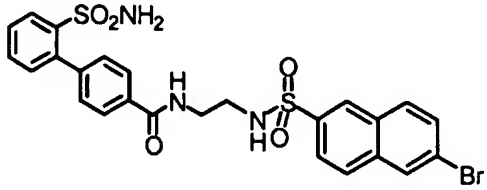
ES-MS $[M+H]^+$ m/z = 505.05



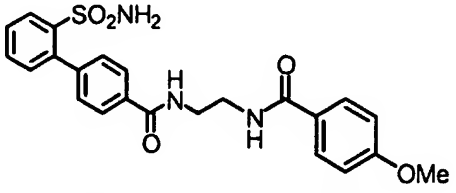
ES-MS $[M+H]^+$ m/z = 577.00 and 579.05



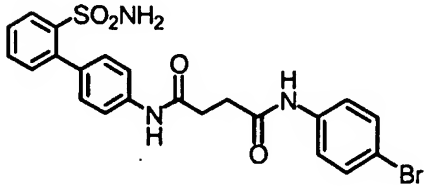
ES-MS $[M+H]^+$ m/z = 552.05 and 554.05



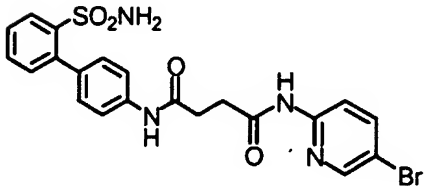
ES-MS $[M+H]^+$ m/z = 590.0



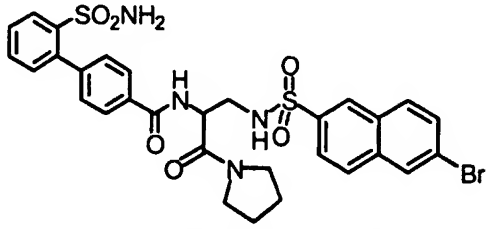
ES-MS $[M+H]^+$ m/z = 454.1



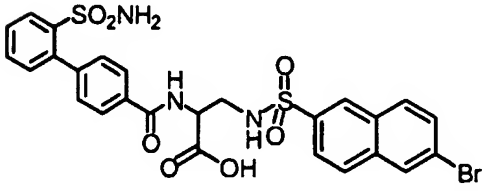
ES-MS $[M+H]^+$ m/z = 503.0 and 504.0



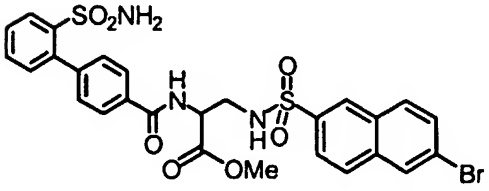
ES-MS $[M+H]^+$ m/z = 505.0



ES-MS $[M+H]^+$ m/z =687.0



ES-MS $[M+H]^+$ m/z = 632.0 and 634.0

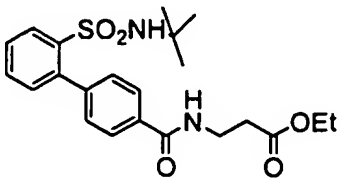


ES-MS $[M+H]^+$ m/z = 646.0 and 648.0

Examples 24-26 below are working examples for making compounds similar to the compound examples 2-23, as set forth above.

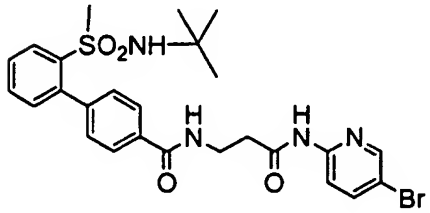
Example 24

Step 1:



To a solution of 4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)benzoic acid (333mg, 1mmol) and β-alanine ethyl ester (154mg, 1mmol) in dimethylformamide (5ml) was added BOP reagent (531mg, 1.2mmol) and triethylamine (279ul, 2mmol). The reaction mixture was stirred at r.t. overnight. After the evaporation of the solvent in vacuo, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give ethyl 3-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}propanoate as a solid (320mg, 74%). MS found for C22H28N2O5S (M+H)+=433.5.

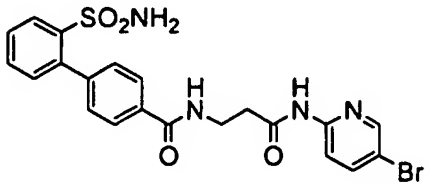
Step 2:



To a solution of ethyl 3-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}propanoate (160mg, 0.37mmol) and 2-amino-5-bromopyridine (64mg, 0.37mmol) in dichloromethane (2ml) was added 2M trimethylaluminum in hexane (0.56ml, 1.1mmol). The mixture was stirred at r.t. overnight. 1N hydrochloride was added to acidify the solution to

PH=2. After the addition of water and dichloromethane, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using solvent system 30% ethyl acetate in hexane as eluent to give 3-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}-N-(5-bromo(2-pyridyl))propanamide (30mg, 15%). MS found for C25H27BrN4O4S M+=559.5, (M+2)+=561.5

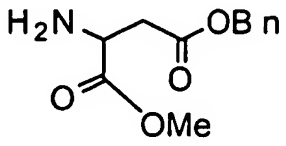
Step 3:



3-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}-N-(5-bromo(2-pyridyl))propanamide (30mg, 0.054mmol) was dissolved in trifluoroacetic aicd (3ml). The reaction mixture was stirred a t r.t. for 3hr. After the evaporation of the solvent in vacuo, the crude residue was purified by RP-HPLC to give N-(5-bromo(2-pyridyl))-3-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}propanamide (22mg, 80%). MS found for C21H19BrN4O4S M+=503.4, (M+2)+=505.4

Example 25

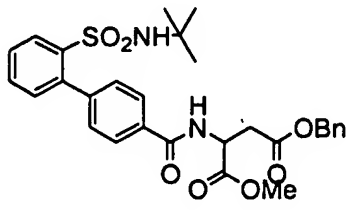
Step 1:



To a solution of N-boc-D-asparic acid (500mg, 1.5mmol), N-boc-L-asparic acid (500mg, 1.5mmol), triethylamine (0.86ml, 6.2mmol) and dimethylaminepyridine

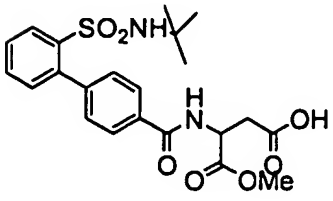
(0.19g, 1.5mmol) in dichloromethame (2ml) at 0 oC was added methyl chloroformate (0.29ml, 3.7mmol). The reaction mixture was stirred at 0 oC and gradually to r.t. for 1hr. Water (5ml) was added. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. The crude product was treated with 4N hydrochloride in dioxane (6ml, 24mmol) for 2hr. After the evaporation of the solvent in vacuo, methyl phenylmethyl 2-aminobutane-1,4-dioate (0.98g, 100%) was obtained. MS found for C12H15NO4 (M+H)+=238.3.

Step 2:



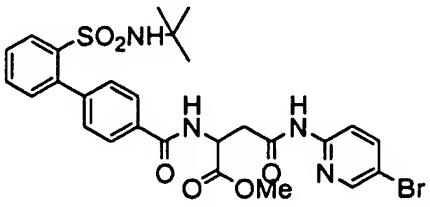
To a solution of 4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)benzoic acid (5g, 15mmol) and methyl phenylmethyl 2-aminobutane-1,4-dioate (4.28g, 18mmol) in dimethylformamide (10ml) was added BOP reagent (7.97g, 18mmol) and triethylamine (4.19ml, 30mmol). The reaction mixture was stirred at r.t. overnight. After the evaporation of the solvent in vacuo, the crude residue was purified by silica gel column chromatography using solvent system 20% ethyl acetate in hexane as eluent to give methyl phenylmethyl 2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}butane-1,4-dioate (7g, 85%). MS found for C29H32N2O7S (M+H)+=553.6.

Step 3:



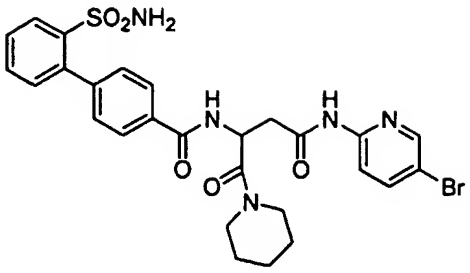
To a solution of methyl phenylmethyl 2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}butane-1,4-dioate (7g, 12.7mmol) in methanol (20ml) was added 10% palladium on carbon (700mg). The mixture was applied with hydrogen balloon overnight. After the filtration with the Celite, the filtrate was concentrated in vacuo to give 3-(methoxycarbonyl)-3-{[4-(2-{[(methylethyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}propanoic acid (5.66g, 96.5%). MS found for C22H26N2O7S (M+H)+=463.5.

Step 4:



To a solution of 3-(methoxycarbonyl)-3-{[4-(2-{[(methylethyl)amino]sulfonyl}-phenyl)phenyl]carbonylamino}propanoic acid (5.66g, 12.1mmol) in dichloromethane (10ml) was added oxalyl chloride (2.11, 24.3mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (10ml). 2-amino-5-bromopyridine (2.52g, 14.6mmol) and pyridine (2.94ml, 36.4mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give methyl 2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}-3-[N-(5-bromo(2-pyridyl))carbamoyl]propanoate (3.2g, 43%). MS found for C27H29BrN4O6S M+=617.5, (M+2)+=619.5.

Step 5:



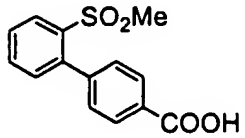
To a solution of methyl 2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-carbonylamino}-3-[N-(5-bromo(2-pyridyl))carbamoyl]propanoate (150mg, 0.24mmol) in methanol (2ml) was added 1N lithium hydroxide (0.49ml, 0.49mmol). The reaction mixture was stirred at r.t. for 2hr. 1N hydrochloride was added to acidify it to PH=2. Dichloromethane was added to extract. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in dimethylformamide (5ml). Piperidine (29ul, 0.29mmol), BOP reagent (127mg, 0.29mmol) and triethylamine (67ul, 0.48mmol) were added. The reaction mixture was stirred overnight. After the evaporation of the solvent in vacuo, the residue was dissolved in trifluoroacetic acid. The reaction mixture was stirred at r.t. overnight. After the concentration, the crude product was purified by RP-HPLC to give N-(5-bromo(2-pyridyl))-4-oxo-4-piperidyl-3-{[4-(2-sulfamoylphenyl)phenyl]-carbonylamino}butanamide (28mg, 19%). MS found for C27H28BrN5O5S M+=614.5, (M+2)+=616.5

Example 26

Step 1:

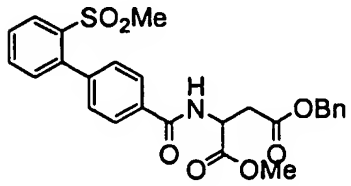
To a solution of 2-bromothioanisole (4.8g, 23.6mmol) and 4-carboxybenzeneboronic acid (3.92g, 23.6mmol) in dioxane (50ml), water (50ml) and 2M potassium carbonate (35.5ml, 71mmol) was added dichlorobis(triphenylphosphine palladium (II) (830mg, 1.2mmol). The reaction mixture was refluxed for 2hr. After the evaporation of the solvent in vacuo, the residue was neutralized by 1N hydrochloride and extracted with dichloromethane. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo to give 4-(2-methylthiophenyl)benzoic acid (5.9g, 100%). MS found for C14H12O2S (M+H)+=245.3.

Step 2:



To a solution of 4-(2-methylthiophenyl)benzoic acid (3.43g, 14mmol) in water (20ml) and acetone (20ml) was added oxone (34.6g, 56mmol). The reaction mixture was stirred overnight. The precipitate was washed with a little amount of dichloromethane to give 4-[2-(methylsulfonyl)phenyl]benzoic acid (2.16g, 63%). MS found for C14H12O4S (M+H)+=277.3.

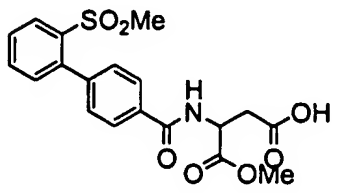
Step 3:



To a solution of 4-[2-(methylsulfonyl)phenyl]benzoic acid (1.36g, 4.95mmol) and methyl phenylmethyl 2-aminobutane-1,4-dioate (1.64g, 7.03mmol) in dimethylformamide (5ml) was added BOP reagent (3.11g, 7.03mmol) and triethylamine (1.63ml, 11.71mmol). The reaction mixture was stirred at r.t. overnight. After the evaporation of the solvent in vacuo, the crude residue was purified by silica gel column chromatography using solvent system 20% ethyl

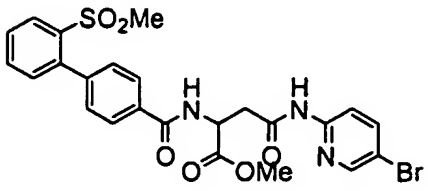
acetate in hexane as eluent to give methyl phenylmethyl 2-({4-[2-(methylsulfonyl)phenyl]phenyl}carbonylamino)butane-1,4-dioate (1.65g, 84%). MS found for C25H25NO7S (M+H)+=496.5.

Step 4:



To a solution of methyl phenylmethyl 2-({4-[2-(methylsulfonyl)phenyl]phenyl}-carbonylamino)butane-1,4-dioate (1.65g, 3.3mmol) in methanol (5ml) was added 10% palladium on carbon (165mg). The mixture was applied with hydrogen balloon for 2hr. After the filtration with the Celite, the filtrate was concentrated in vacuo to give 3-(methoxycarbonyl)-3-({4-[2-(methylsulfonyl)phenyl]phenyl}carbonyl-amino)propanoic acid (1.39g, 100%). MS found for C19H19NO7S (M+H)+=406.4.

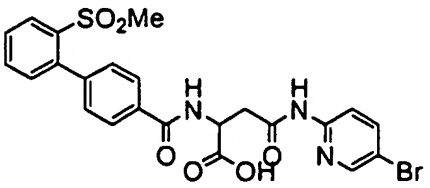
Step 5:



To a solution of 3-(methoxycarbonyl)-3-({4-[2-(methylsulfonyl)phenyl]phenyl}-carbonylamino)propanoic acid (1.36g, 3.36mmol) in dichloromethane (7ml) was added oxalyl chloride (587ul, 6.73mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (7ml). 2-amino-5-bromopyridine (0.7g, 4.04mmol) and pyridine (816ul, 10.09mmol) were added to the solution. The

mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give methyl 3-[N-(5-bromo(2-pyridyl))-carbamoyl]-2-({4-[2-(methylsulfonyl)phenyl]phenyl}carbonylamino)propanoate (400mg, 21%). MS found for C24H22BrN3O6S M+=560.4, (M+2)+=561.4.

Step 6:



To a solution of methyl 3-[N-(5-bromo(2-pyridyl))carbamoyl]-2-({4-[2-(methyl-sulfonyl)phenyl]phenyl}carbonylamino)propanoate (30mg, 0.054mmol) in methanol (2ml) was added 1N lithium hydroxide (107ul, 0.107mmol). The reaction mixture was stirred for 2hr. 1N hydrochloride was added to acidify it to PH=2. Dichloro-methane was added to extract. The organic layer was separated, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by RP-HPLC to give methyl 3-[N-(5-bromo(2-pyridyl))carbamoyl]-2-({4-[2-(methyl-sulfonyl)phenyl]phenyl}carbonylamino)propanoic acid (7g, 24%). MS found for C23H20BrN3O6S (M+H)+=547.4.

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of this invention is guided by in vitro protease activity assays (see below) and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μM. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the

enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC_{50} of a compound is determined from the substrate turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC_{50} of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC_{50} of less than 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC_{50} of greater than 1.0 μM in the thrombin assay, preferably greater than 10.0 μM, and more preferred compounds have an IC_{50} of greater than 100.0 μM in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and were determined using the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma free system with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μM) in 20 mM Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM $CaCl_2$ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor

mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Eight different concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex are used for determination of percent inhibition.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. et al., Thromb. Haemost. 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

Effects of Compounds in Rabbit Venous Thrombosis model

Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at the higher doses evaluated. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 μg/kg + 2.57 μg/kg/min). Compounds have no significant effects on hematological parameters as compared to saline controls. All measurements are

an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean ± SD.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of the formula:

A-Q-D-E-G-J-X

wherein:

A is a member selected from the group consisting of:

(a) phenyl which is substituted with 0-3 R^1 groups;

(b) naphthyl, which is substituted with 0-3 R^1 groups; and

(c) an aromatic or non-aromatic 5-10 membered heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and is substituted with 0-2 R^1 groups;

R^1 is a member selected from the group consisting of:

halo, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -NO_2, -$(CH_2)_m$-NR^2R^3, -NHR^2R^3, -$C(=O)$-NR^2R^3, -$C(=O)$-OR^2, -$S(=O)_2$-NR^2R^3, -$S(=O)_2$-R^2, -CF_3, -$(CH_2)_m$-OR^2, a carbocyclic aryl group and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^2 and R^3 are independently selected from:

H, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and -C_{0-6}alkyl-carbocyclic aryl, or R^2 and R^3 together with the N atom to which they are attached can form a 5 to 8 membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of O, N and S; wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -$S(=O)_2$-OH, -CN, -CF_3 and -NO_2;

m is an integer of 0-3;

Q is a member selected from the group consisting of:

a direct link; divalent C_1-C_4alkyl; divalent C_2-C_4alkynyl; divalent C_{2-4}alkenyl; -C(=O)-; -C(=N-R^4)-, -N(-R^4)-, -NR^4-CH_2-, -C(=O)-N(-R^4)-, -N(-R^4)-C(=O)-, -S(=O)$_2$-, -O-, -S(=O)$_2$-N(-R^4)- and –N(-R^4)-S(=O)$_2$-, wherein one or more hydrogens on each of the divalent C_1-C_4alkyl, divalent C_2-C_4alkynyl and divalent C_{2-4}alkenyl moieties can be replaced with a R^4 group;

R^4 is a member selected from the group consisting of:

H, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and -C_{0-6}alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -S(=O)$_2$-OH, -CN, -CF_3 and -NO_2;

D is a member selected from the group consisting of:

(a) phenyl substituted with 0-2 R^{1a} groups; and

(b) an aromatic or non-aromatic 5-10 membered heterocyclic ring system which may be a monocyclic ring system or a fused bicyclic ring system, wherein the heterocyclic ring system contains 1-4 heteroatoms selected from N, O and S and the ring system is substituted with 0-2 R^{1a} groups;

R^{1a} is a member selected from the group consisting of:

halo, -C_{1-6}alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, -S(=O)$_2$-OH, -CN, -NO_2, -$(CH_2)_n$-N$R^{2a}R^{3a}$,

$-S(=O)_2NR^{2a}R^{3a}$, $-S(=O)_2-R^{2a}$, $-CF_3$, $-(CH_2)_n-OR^{2a}$, $-C(=O)-O-R^{2a}$, $-C(=O)NR^{2a}R^{3a}$, and a 5-6 membered aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the aromatic heterocyclic ring and the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $-CN$, $-CF_3$ and $-NO_2$;

n is an integer of 0-2;

R^{2a} and R^{3a} are independently a member selected from the group consisting of: H, $-C_{1-6}$alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $-S(=O)_2-O^-$, $-CN$, $-CF_3$ and $-NO_2$;

E is selected from:

$-(CH_2)_q-C(=O)-$, $-(CH_2)_q-NR^5-C(=O)-(CH_2)_x-$, $-(CH_2)_q-C(=O)-NR^5-(CH_2)_x-$, $-(CH_2)_q-NR^5-CO-NR^6(CH_2)_x-$, and SO_2-;

q and x are independently an integer of 0-2;

R^5 and R^6 are independently a member selected from the group consisting of: H, $-C_{1-6}$acyl, $-C_{1-6}$alkyl, $-C_{1-6}$alkyloxy, $-C_{1-6}$alkyl-$C(=O)-NR^{2b}R^{3b}$, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-6}$alkylC_{3-8}cycloalkyl, $-C_{1-4}$alkyl-$C(=O)-OH$, $-C_{0-6}$alkyl-(carbocyclic aryl), $-C_{0-4}$alkyl-(monocyclic heteroaryl) and $-C_{1-4}$alkyl-$C(=O)-O-C_{1-4}$alkyl, wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl

moiety and the monocyclic heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $-S(=O)_2OH$, -CN, $-CF_3$ and $-NO_2$;

R^{2b} and R^{3b} are independently a member selected from the group consisting of: H, $-C_{1-6}$alkyl, C_{1-6}alkyloxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-6}alkylC_{3-8}cycloalkyl, and $-C_{0-6}$alkyl-(carbocyclic aryl), wherein from 0-4 hydrogen atoms on the ring atoms of the carbocyclic aryl moiety may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $-S(=O)_2-O^-$, -CN, $-CF_3$ and $-NO_2$;

G is $-CHR^6-$ and $-CHR^6-CHR^7-$;

R^6 and R^7 are each a member independently selected from the group consisting of: H, alkyl, $-C_{0-2}$-alkyl-aryl, $-C_{0-2}$-alkyl-heteroaryl, $-C_{0-2}$-alkyl-$C(=O)-OR^8$; $-C_{0-2}$-alkyl-$C(=O)-NR^9R^{10}$; $-C_{0-2}$-alkyl-OR^9; $-C_{0-2}$-alkyl-O-C_{0-2}-alkyl-OR^9; $-C_{0-2}$-alkyl-O-C_{0-2}-alkyl-NR^9R^{10}; $-C_{0-2}$-alkyl-NR^9R^{10}; $-C_{0-2}$-alkyl-$NR^9-C(=O)-R^{10}$; $-C_{0-2}$-alkyl-$NR^9-C(=O)-O-R^{10}$; $-NR^9-C(=O)$ C_{0-2}-alkylaryl; and $-C_{0-2}$-alkyl-$NR^8-C(=O)-NR^9R^{10}$, $-C_{0-2}$-alkyl-$NR^9-SO_2R^{10}$; $-C_{0-2}$-alkyl-$NR^8-SO_2NR^9R^{10}$;

R^8, R^9 and R^{10} are each a member independently selected from the group consisting of:

H, $-C_{1-4}$-alkyl, $-C_{0-4}$-alkyl-carbocyclic aryl; $-C_{0-4}$-acyl; and $-C_{0-4}$-alkyl-heterocycle; or R^8 with R^9 and R^9 with R^{10}, together with the N atom to which they are attached may each independently form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

halo, -C_{1-4}-alkyl, -CN, -NO_2, -C(=O)-$NR^{2d}R^{3d}$, -C(=O)-OR^{2d},
-$(CH_2)_t$-$NR^{2d}R^{3d}$; -SO_2-$NR^{2d}R^{3d}$; -SO_2R^{2d}; -CF_3 and -$(CH_2)_t$-OR^{2d};

t is an integer from 0-3;

R^{2d} and R^{3d} are each independently a member selected from the group consisting of:

H, -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

J is a member selected from the group consisting of:

-C(=O)-N(-R^{11})-; -N(-R^{11})-C(=O)- and –N(-R^{11})-SO_2-;

R^{11} is a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) a fused aromatic heterobicyclic ring system containing 1-4 heteroatoms selected from N, O and S and having 0-3 ring atoms substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; -C_{1-4}-alkyl; carbocyclic aryl; -CN; -C(=O)-OR^{2e}; -C(=O)-$NR^{2e}R^{3e}$;
-NO_2; -$NR^{2e}R^{3e}$; -CH_2-$NR^{2e}R^{3e}$; -SO_2-$NR^{2e}R^{3e}$; -SO_2-R^{2e}; -CF_3; -OR^{2e};
-O-CH_2-C(=O)-OR^{2e}; -NR^{2e}-C(=O)-R^{3e}; -N(-R^{2e})-SO_2-R^{3e};
-CH_2-N(-R^{2e})-C(=O)-R^{3e} and -CH_2-N(-R^{2e})-SO_2-R^{3e};.

R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} is a member selected from the group consisting of:

halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-$NR^{2g}R^{3g}$; -C(=O)-OR^{2g}; -NO_2; -$(CH_2)_s$-$NR^{2g}R^{3g}$; -$SO_2NR^{2g}R^{3g}$; -SO_2R^{2g}; -CF_3; and -$(CH_2)_sOR^{2g}$;

s is an integer from 0-3;

R^{2g} and R^{3g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and pro-drug derivatives, thereof.

2. A compound of claim 1, wherein:

A is a member selected from the group consisting of:

(a) phenyl, which is substituted with 0-2 R^1 groups;

(b) naphthyl, which is substituted with 0-2 R^1 groups; and

(c) an aromatic or non-aromatic heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring system which is substituted with 0-2 R^1 groups;

R^1 is a member selected from the group consisting of:

halo; C_{1-4}-alkyl; a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-NR^2R^3; -C(=O)-OR^2; -NO_2; -$(CH_2)_s$-NR^2R^3; -$SO_2NR^2R^3$; -SO_2R^2; -CF_3; and -$(CH_2)_sOR^2$;

R^2 and R^3 are each independently selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl; or R^2 and R^3 together with the N atom to which they are attached can form a 5 to 8 membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O, and S;

m is an integer of 0-2;

Q is a member selected from the group consisting of:

a direct link; a divalent C_1-C_4-alkyl group; a divalent C_2-C_4-alkynyl group; a divalent C_2-C_4-alkenyl group; -C(=O)-, -C(=N-R^4)-; -N(-R^4)-, -N(-R^4)-CH_2-; -C(=O)-N(-R^4)-; -N(-R^4)-C(=O)-, -SO_2-, -O-, -SO_2-N(-R^4)- and –N(-R^4)-SO_2-;

R^4 is a member selected from the group consisting of:

H, -C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclicaryl;

D is a member selected from the group consisting of:

(a) phenyl substituted with 0-2 R^{1a} groups; and

(b) an aromatic or non-aromatic 5-6 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms on the heterocyclic ring are substituted with 0-2 R^{1a} groups;

R^{1a} is a member selected from the group consisting of:

halo, -C_{1-4}-alkyl, -CN, -NO_2, -C(=O)-$NR^{2a}R^{3a}$, -C(=O)-OR^{2a}; -$(CH_2)_n$-$NR^{2a}R^{3a}$; -SO_2-$NR^{2a}R^{3a}$; -SO_2R^{2a}; -CF_3 and -$(CH_2)_n$-OR^{2a};

n is an integer from 0-2;

R^{2a} and R^{3a} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-(carbocyclic aryl);

E is a member selected from the group consisting of:

-C(=O)-N(-R^5)- and –N(-R^5)-C(=O)-;

R^5 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylcarbocyclicaryl; -C_{0-4}-alkyl-monocyclicheteroaryl; -C_{1-4}-alkyl-C(=O)-OH, -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-$NR^{2b}R^{3b}$;

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{0-4}-alkyl-aryl, and -C_{0-4}-alkyl-heterocyclic group; or R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-$NR^{2c}R^{3c}$; -C(=O)-OR^{2c}; -$(CH_2)_m$-$NR^{2c}R^{3c}$; -SO_2-$NR^{2c}R^{3c}$; -SO_2R^{2c}; -CF_3 and -$(CH_2)_m$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

G is -CHR^6-CHR^7-;

R^6 and R^7 are each a member independently selected from the group consisting of:

H, alkyl, -C_{0-2}-alkyl-aryl, -C_{0-2}-alkyl-heteroaryl, -C_{0-2}-alkyl-C(=O)-OR^8; -C_{0-2}-alkyl-C(=O)-NR^9R^{10}; -C_{0-2}-alkyl-O-R^9; -C_{0-2}-alkyl-O-C_{2-4}-alkyl-O-R^9; -C_{0-2}-alkyl-O-C_{2-4}-alkyl-NR^9R^{10}; -C_{0-2}-alkyl-NR^9R^{10}; -C_{0-2}-alkyl-N(-R^9)-C(=O)-R^{10}; -C_{0-2}-alkyl-N(-R^9)-C(=O)-OR^{10};

$-C_{0-2}$-alkyl-N(-R^8)-C(=O)-NR^9R^{10}, $-C_{0-2}$-alkyl-N(-R^9)-SO_2-R^{10}; and
$-C_{0-2}$-alkyl-N(-R^8)-SO_2-NR^9R^{10};

R^8, R^9 and R^{10} are each a member independently selected from the group consisting of:

H, $-C_{1-4}$-alkyl, $-C_{0-4}$-alkyl-carbocyclic aryl; and $-C_{0-4}$-alkyl-heterocycle; or R^9 with R^{10}, together with the N atom to which they are attached may each independently form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

halo, $-C_{1-4}$-alkyl, -CN, $-NO_2$, -C(=O)-$NR^{2d}R^{3d}$, -C(=O)-OR^{2d}, $-(CH_2)_t$-$NR^{2d}R^{3d}$; $-SO_2$-$NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$ and $-(CH_2)_t$-OR^{2d};

t is an integer from 0-2;

R^{2d} and R^{3d} are each independently a member selected from the group consisting of:

H, $-C_{1-4}$-alkyl and $-C_{1-4}$-alkyl-aryl;

J is a member selected from the group consisting of:

-C(=O)-N(-R^{11})-; -N(-R^{11})-C(=O)- and –N(-R^{11})-SO_2-;

R^{11} is a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl and $-C_{0-4}$-alkyl-carbocyclic aryl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups;

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) a fused aromatic heterobicyclic ring system containing 1-4 heteroatoms selected from N, O and S and having 0-3 ring atoms substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:
Halo; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-CN; -C_{0-2}-C(=O)-OR^{2e}; -C_{0-2}-C(=O)-$NR^{2e}R^{3e}$; -C_{0-2}-NO_2; -C_{0-2}-$NR^{2e}R^{3e}$; -CH_2-$NR^{2e}R^{3e}$; -C_{0-2}-SO_2-$NR^{2e}R^{3e}$; -C_{0-2}-SO_2-R^{2e}; trihaloalkyl; -C_{0-2}-OR^{2e}; -O-CH_2-C(=O)-OR^{2e}; -C_{0-2}-N(-R^{2e})-C(=O)-R^{3e}; -C_{0-2}-N(-R^{2e})-SO_2-R^{3e}; -CH_2-N(-R^{2e})-C(=O)-R^{3e} and -CH_2-N(-R^{2e})-SO_2-R^{3e};

R^{2e} and R^{3e} are each independently a member selected from the group consisting of: H; -C_{1-4}-alkyl; -C_{1-4}-alkyl-carbocyclic aryl; and -C_{1-4}-alkyl-heterocyclic; or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} is a member selected from the group consisting of:
halo; -C_{1-4}-alkyl; a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-$NR^{2g}R^{3g}$; -C(=O)-OR^{2g}; -NO_2; -$(CH_2)_s$-$NR^{2g}R^{3g}$; -$SO_2NR^{2g}R^{3g}$; -SO_2R^{2g}; -CF_3; and -$(CH_2)_s$$OR^{2g}$;

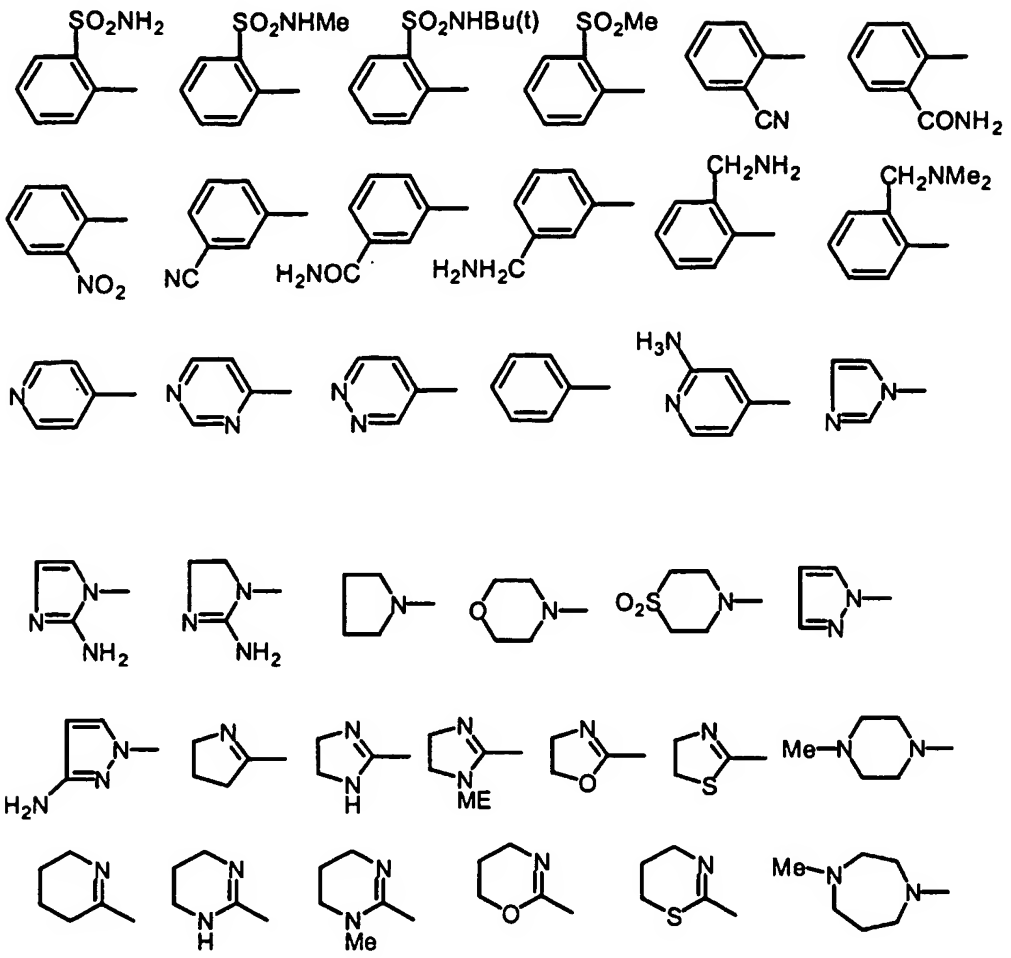
s is an integer from 0-2;

R^{2g} and R^{3g} are each independently selected from the group consisting of:
H; C_{1-4}-alkyl and -C_{0-4}-alkyl-(carbocyclic aryl);

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

3. A compound of claim 1, wherein:

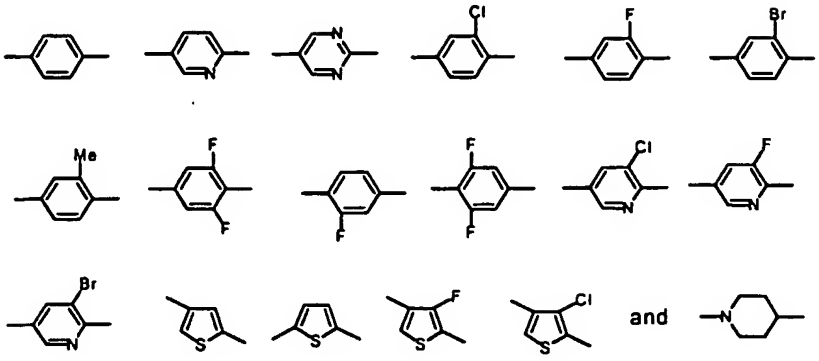
A is a member selected from the group consisting of:



Q is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(CH_3)-; -N(CH_3)-CH_2-; -C(=NH)- and -CH_2-;

D is a member selected from the group consisting of:

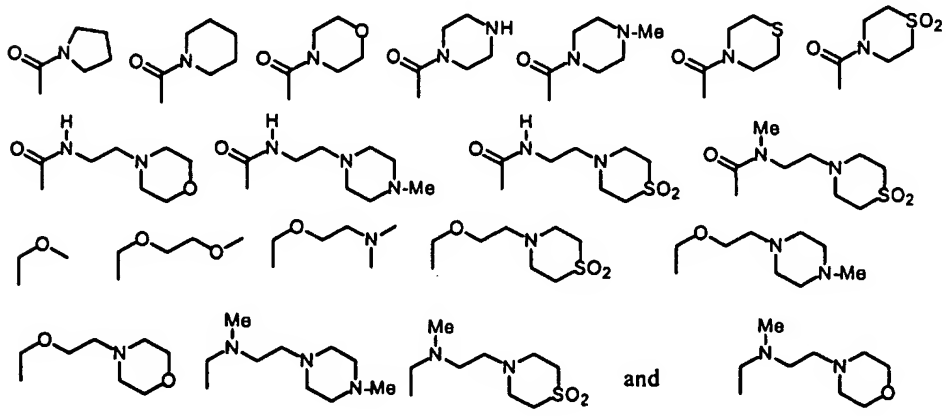


E is a member selected from the group consisting of:

-NH-C(=O)-and -C(=O)-NH-;

G is $-CHR^6-CHR^7-$, wherein R^6 and R^7 are each independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$; $-(CH_2)_2-COOH$; -COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-NH_2$; -NH-Ac, -NH-C(=O)-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bn; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; $-NH-SO_2-Me$; $-NH-SO_2-Bu$; $-NH-SO_2-Ph$; $-NH-SO_2-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-O-Ac$; and



J is a member selected from the group consisting of:

-C(=O)-NH-; -NH-C(=O)- and -NH-SO_2-;

X is a member selected from the group consisting of:

(a) phenyl, which can be substituted with 0-3 R^{1e} groups;

(b) naphthyl, which can be substituted with 0-3 R^{1e} groups;

(c) pyridyl, which can be substituted with 0-3 R^{1e} groups; and

(d) pyrimidinyl, which can be substituted with 0-3 R^{1e} groups;

R^{1e} is in each occurrence independently a member selected from the group consisting of:

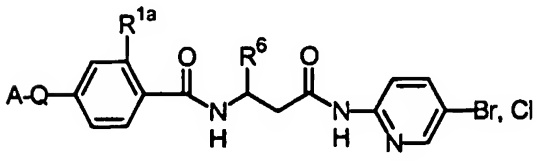
-Cl; -Br; -F; -I; -OH; -OMe; -COOH; -COOEt; -C(=O)-NH_2;

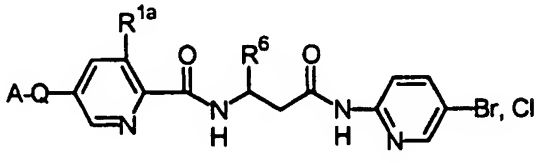
-C(=O)-NH-Me; -C(=O)-N(-Me)$_2$; -CN; -NO_2; -NH_2; -NH-Me; -CH_2-NH_2;

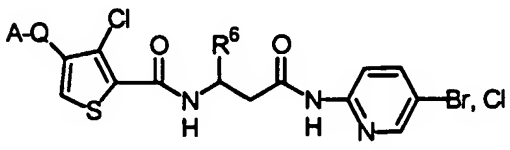
-CH_2-NH-Me; -SO_2-Me; -SO_2-NH_2; and -SO_2-NH-Me,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

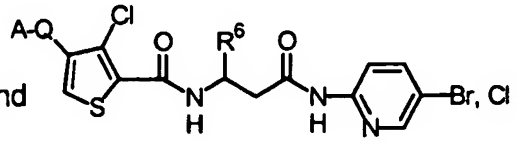
4. A compound of claim 1 selected from the group consisting of:



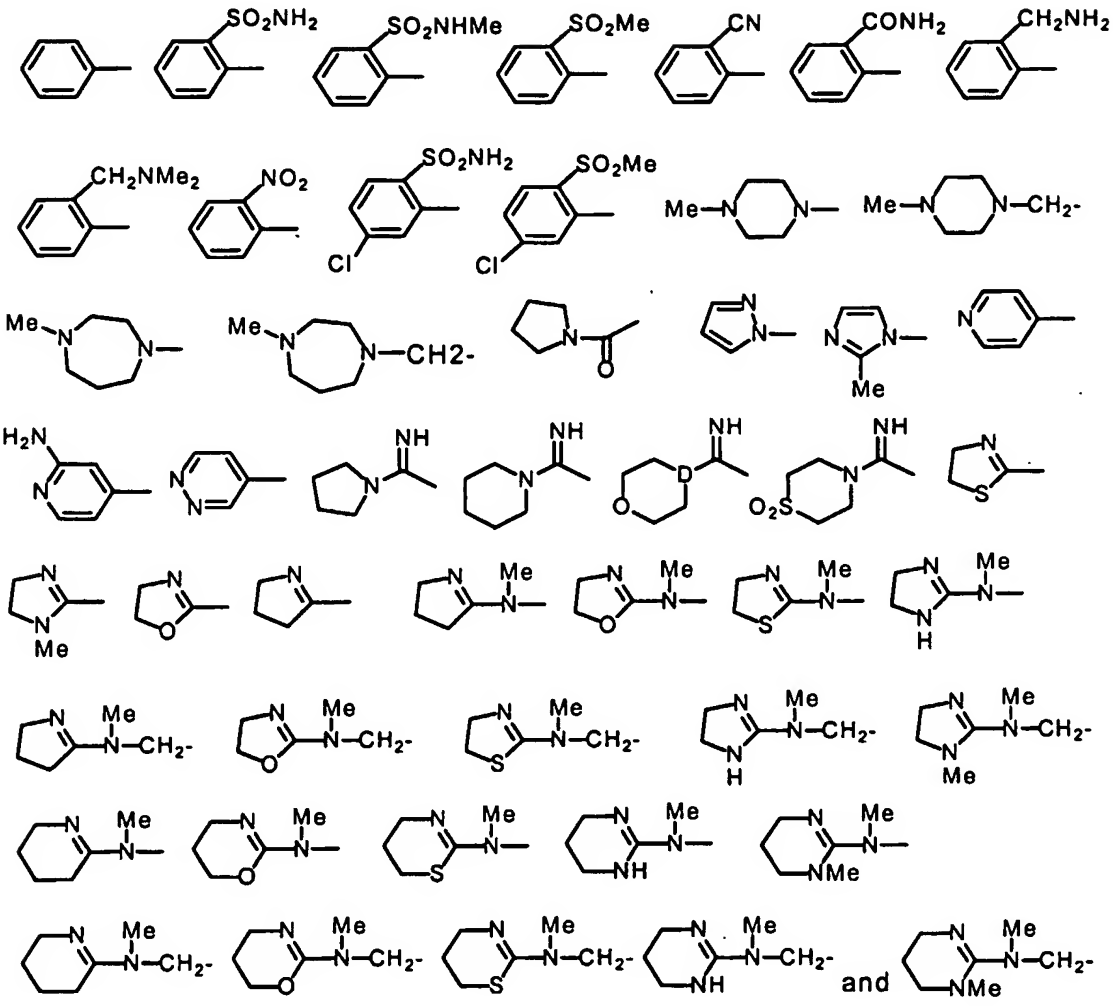




and



wherein the A-Q portion for each of the above formulae is independently a member selected from the group consisting of:

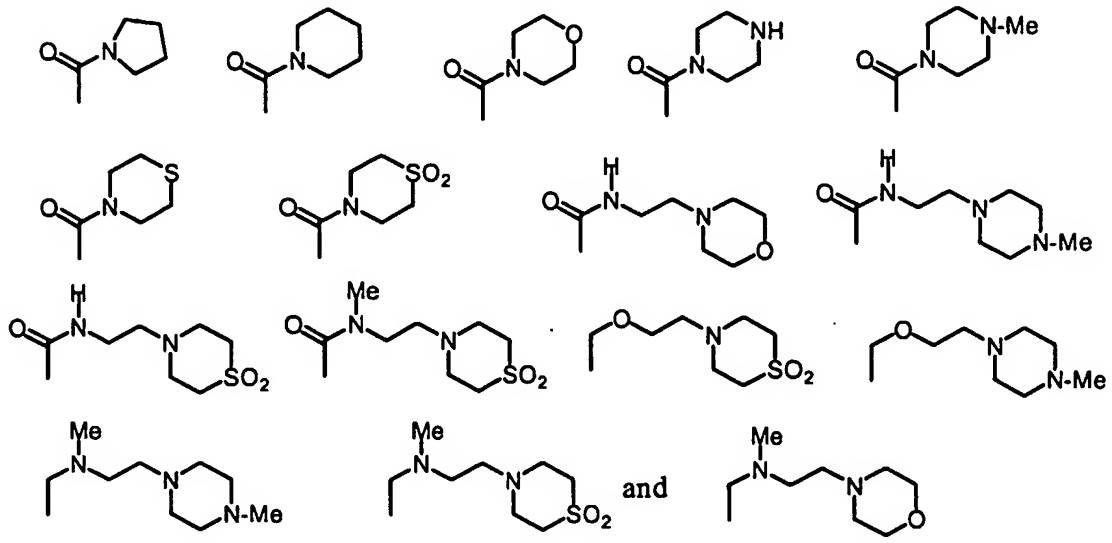


R^{1a} on the phenyl and pyridyl portions of the above formulae is independently selected from the group consisting of:

-H; -Cl; -F; -Br; -Me; -O-Me; -NO_2; -COOH; -CN; -C(=O)-NH_2; and -C(=O)-O-Me;

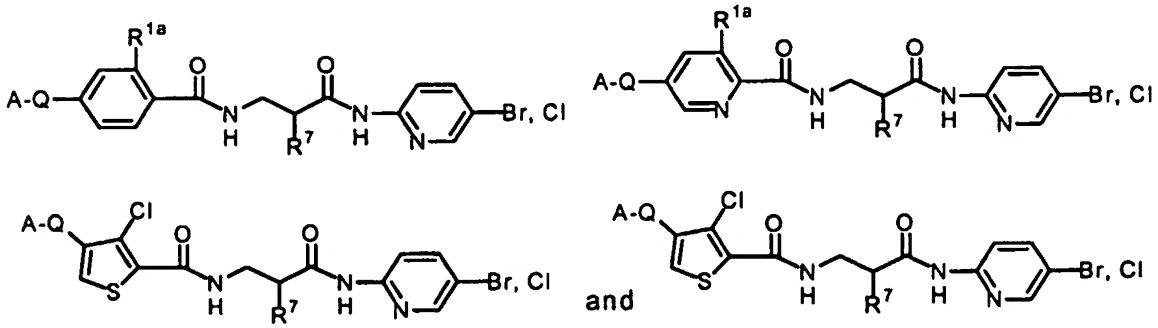
R^6 for each of the above formulae is independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$;
$-COO-Et$; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;
$-CH_2-O-CH_2-CH_2-O-Me$; and $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

5. A compound of claim 1 selected from the group consisting of:



wherein:

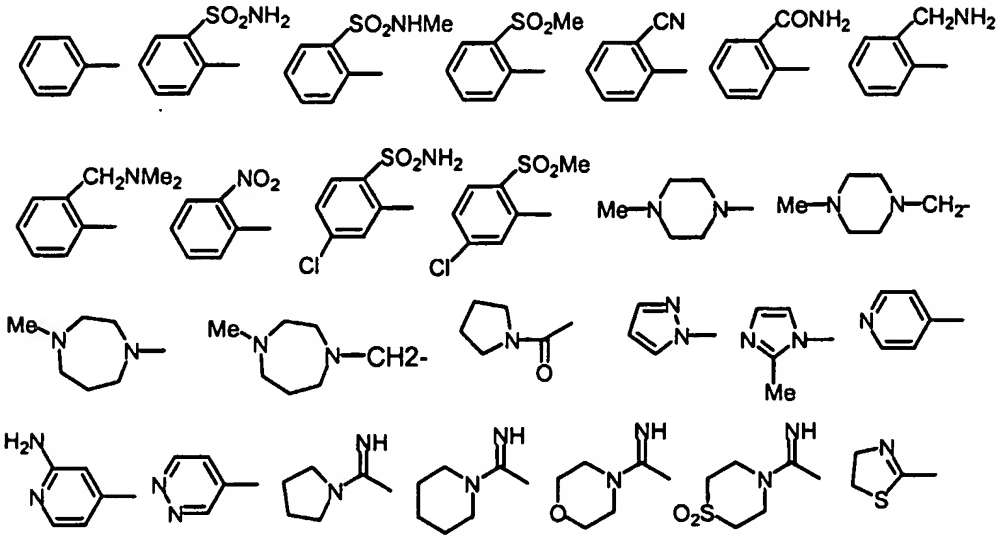
R^{1a} is a member selected from the group consisting of:

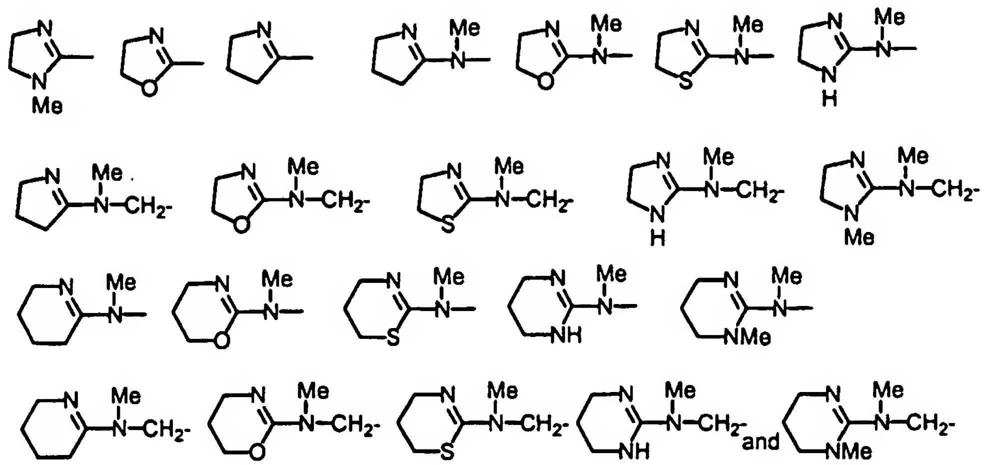
H; -Cl; -F; -Br; -Me; -O-Me; -NO_2; -C(=O)-OH; -CN; -C(=O)-NH_2 and -C(=O)-O-Me;

R^7 is a member selected from the group consisting of:

H; -NH_2; -NH-C(=O)-Me; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; -NH-C(=O)-O-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bu; -NH-SO_2-Me; -NH-SO_2-Me; -NH-SO_2-Ph; -NH-SO_2-NH-Me and -NH-SO_2-N(-Me)$_2$;

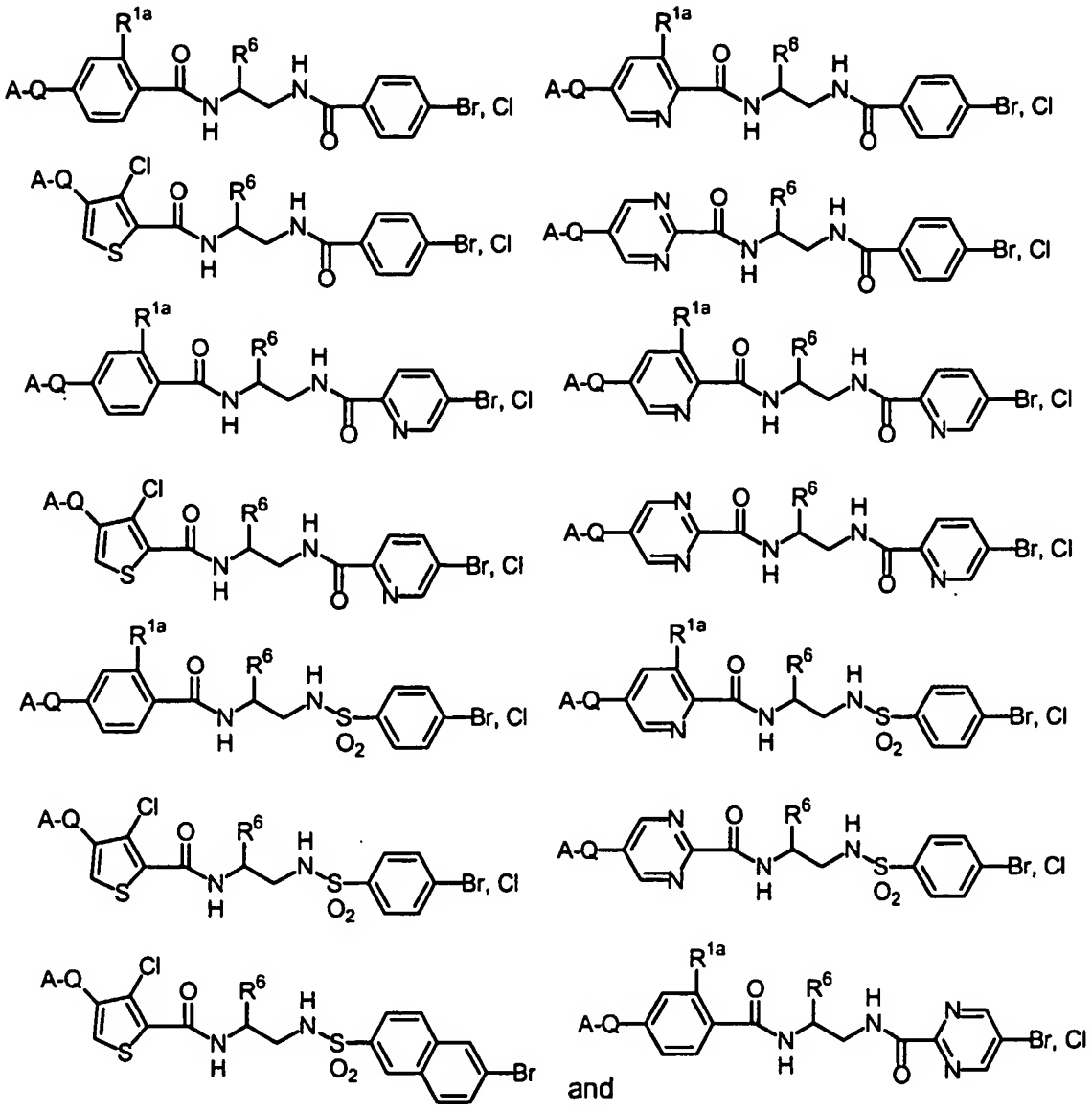
wherein A-Q in each formula is independently a member selected from the group consisting of:





and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

6. A compound of claim 1 selected from the group consisting of:



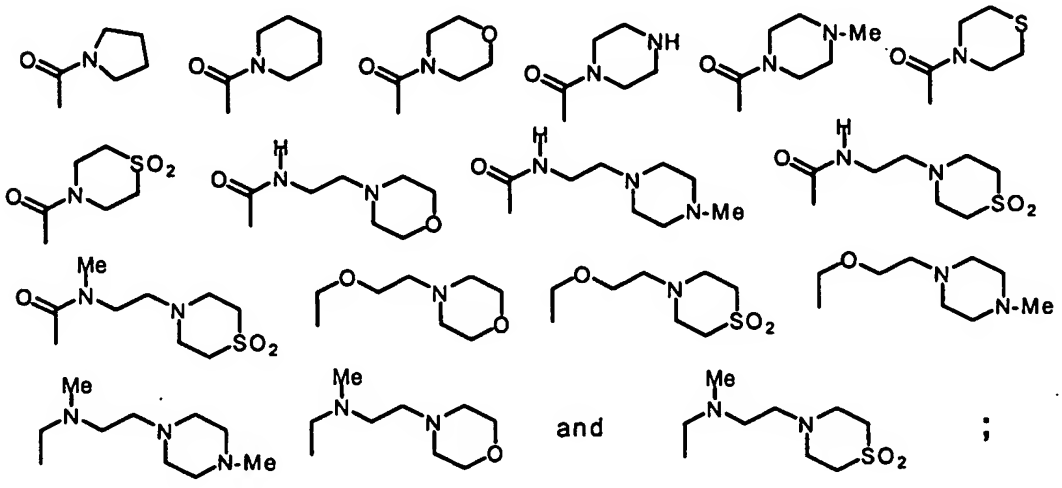
wherein:

R^{1a} is a member independently selected from the group consisting of:

H; -Cl; -F; -Br; -Me; -O-Me; $-NO_2$; -COOH; -CN, $-C(=O)-NH_2$ and -C(=O)-O-Me;

R^6 is independently a member selected from the group consisting of:

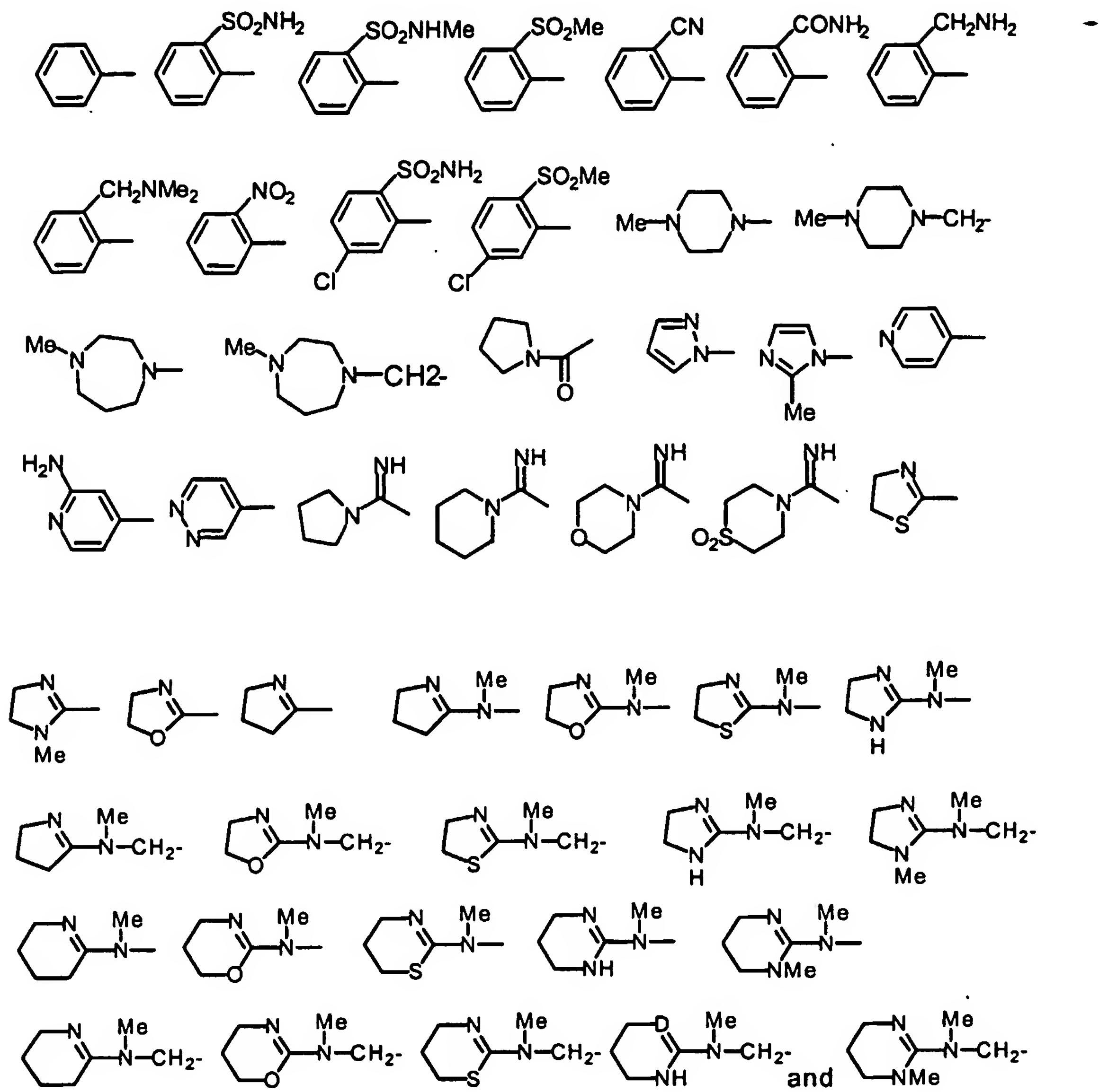
H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$; $-COO-Et$; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$; $-CH_2-O-CH_2-CH_2-O-Me$; and $-CH_2-O-CH_2-CH_2-N(-Me)_2$;



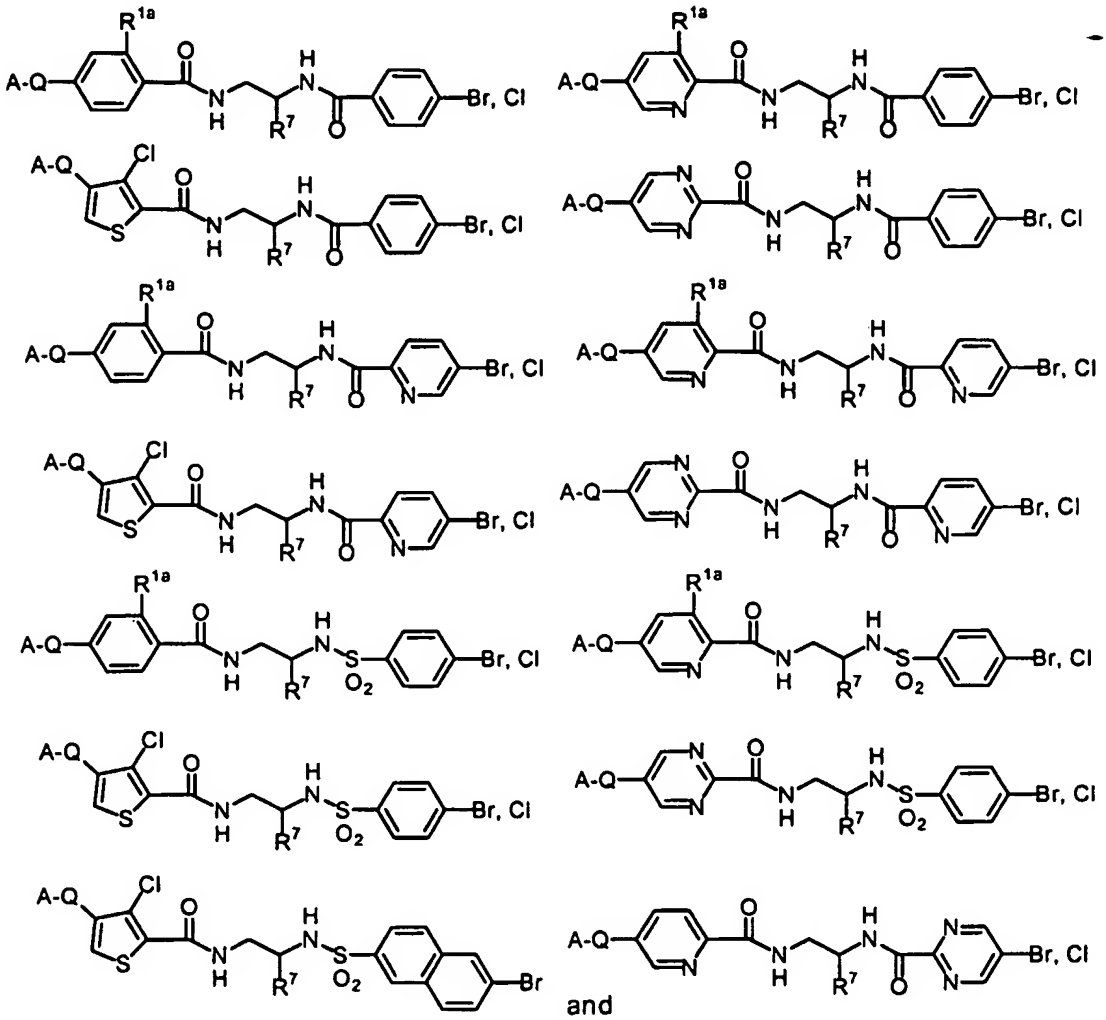
;

5

where A-Q is a member selected from the group consisting of:



7. A compound of claim 1 selected from the group consisting of:



and

wherein:

R^{1a} is a member selected from the group consisting of:

H; -Cl; -F; -Br; -Me; -O-Me; $-NO_2$; -C(=O)-OH; -CN; $-C(=O)-NH_2$ and -C(=O)-O-Me;

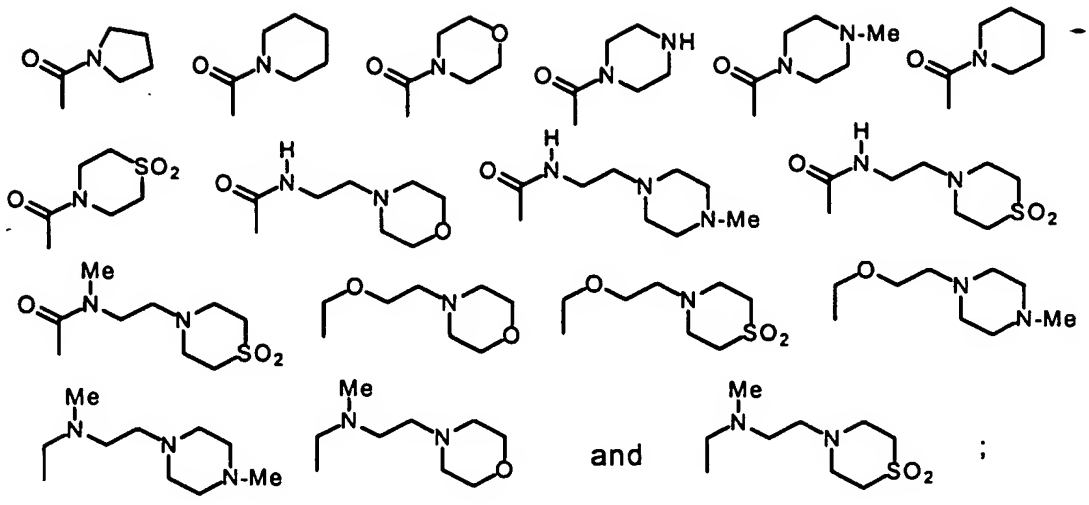
R^7 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$;

-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

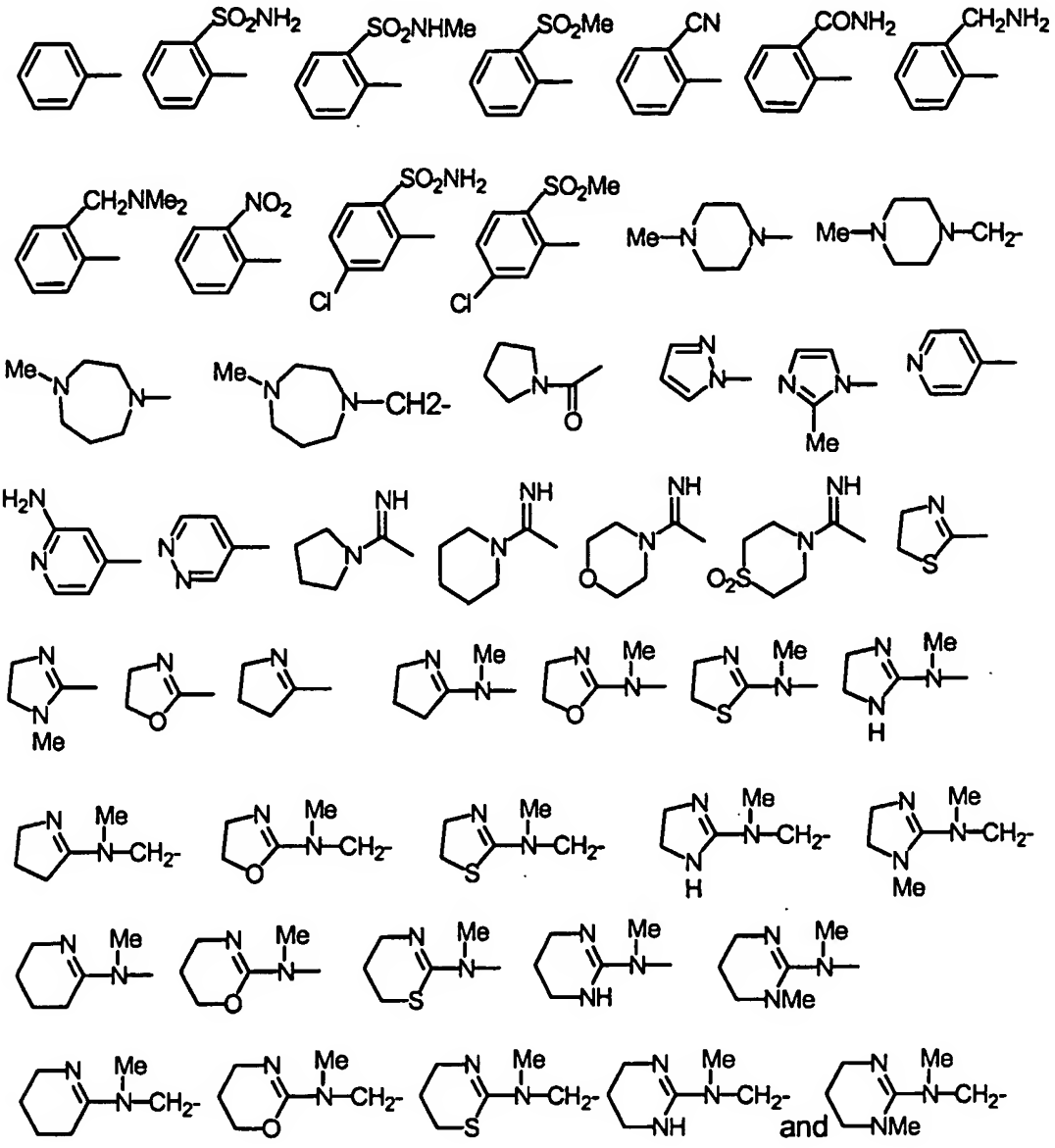
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$; and


and

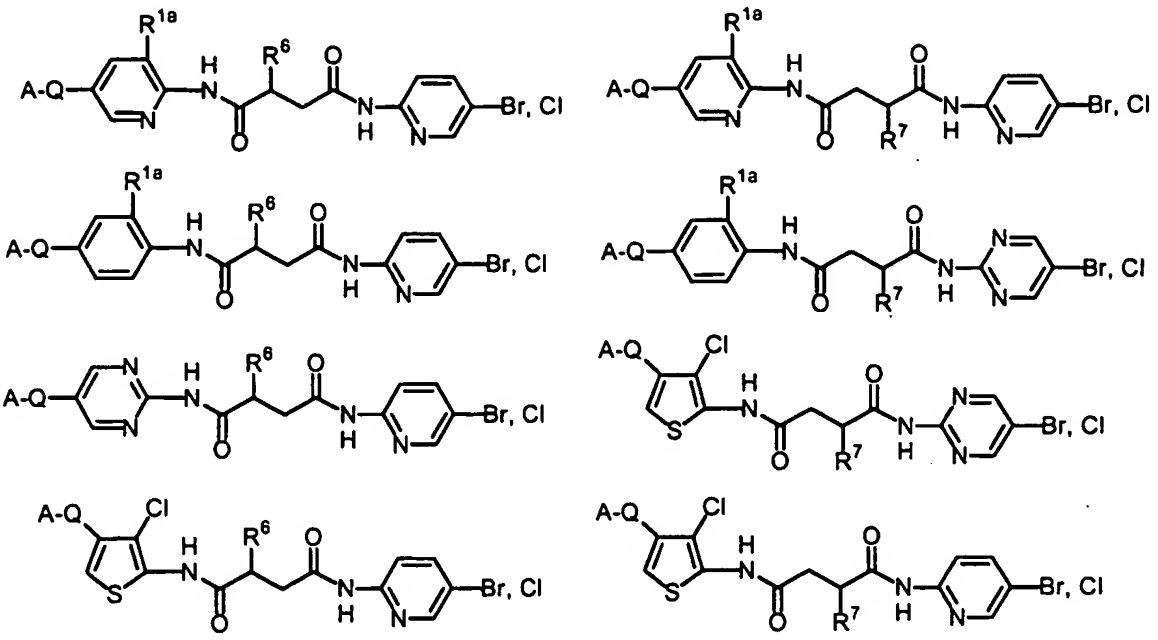
;

A-Q for each of the formulae is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

8. A compound of claim 1 selected from the group consisting of:



wherein

R^{1a} is a member independently selected from the group consisting of:

H, Cl, F, Br, I, NO_2, OMe, Me, COOH, COO-(C_1-C_6 alkyl), $CONH_2$;

R^6 and R^7 are independently selected from:

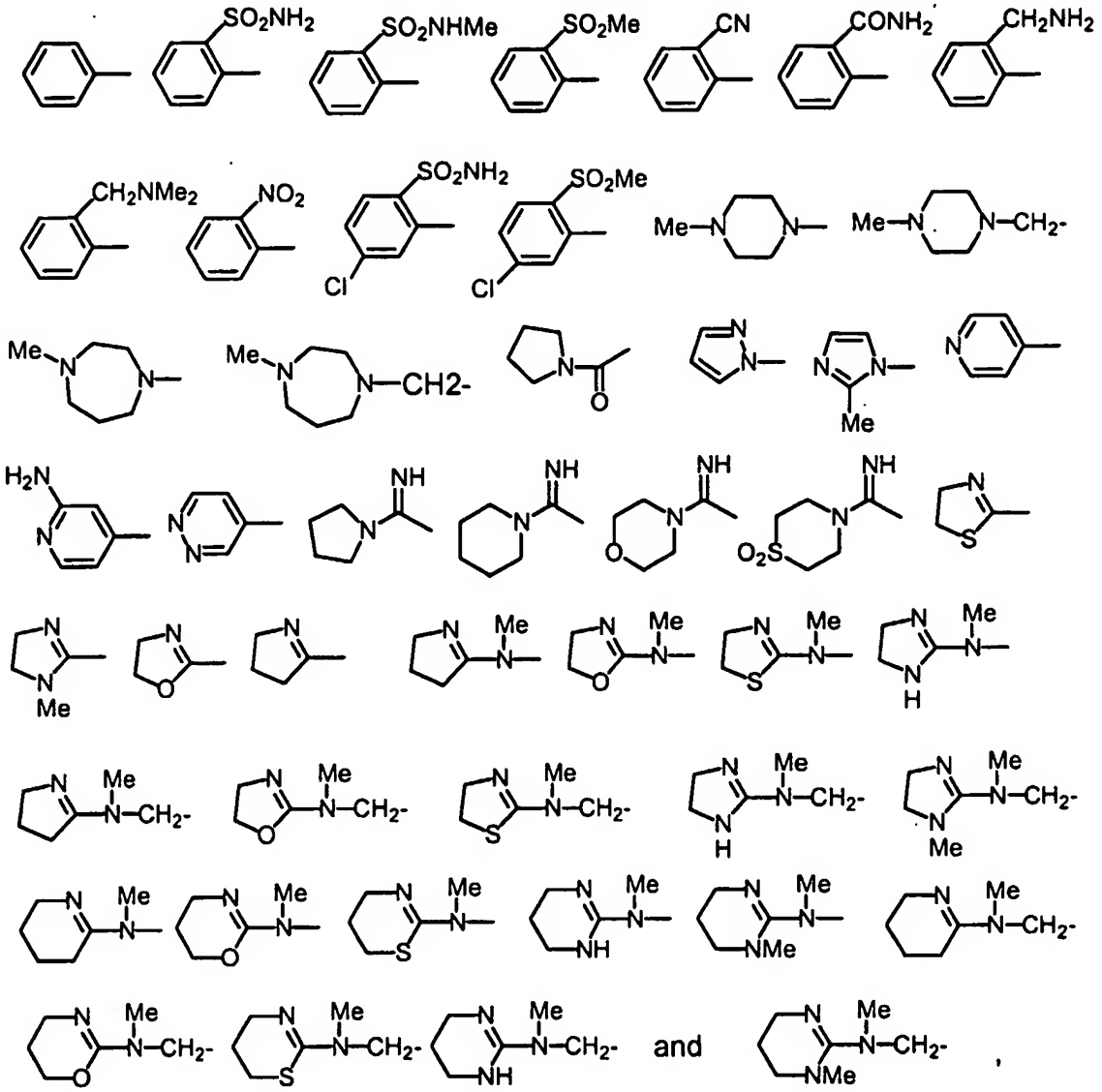
H; $-NH_2$; -NH-C(=O)-Me; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu;

-NH-C(=O)-O-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bu;

-NH($-SO_2$)-Me; -NH-SO_2-Me; -NH-SO_2-Ph; -NH-SO_2-NH-Me and

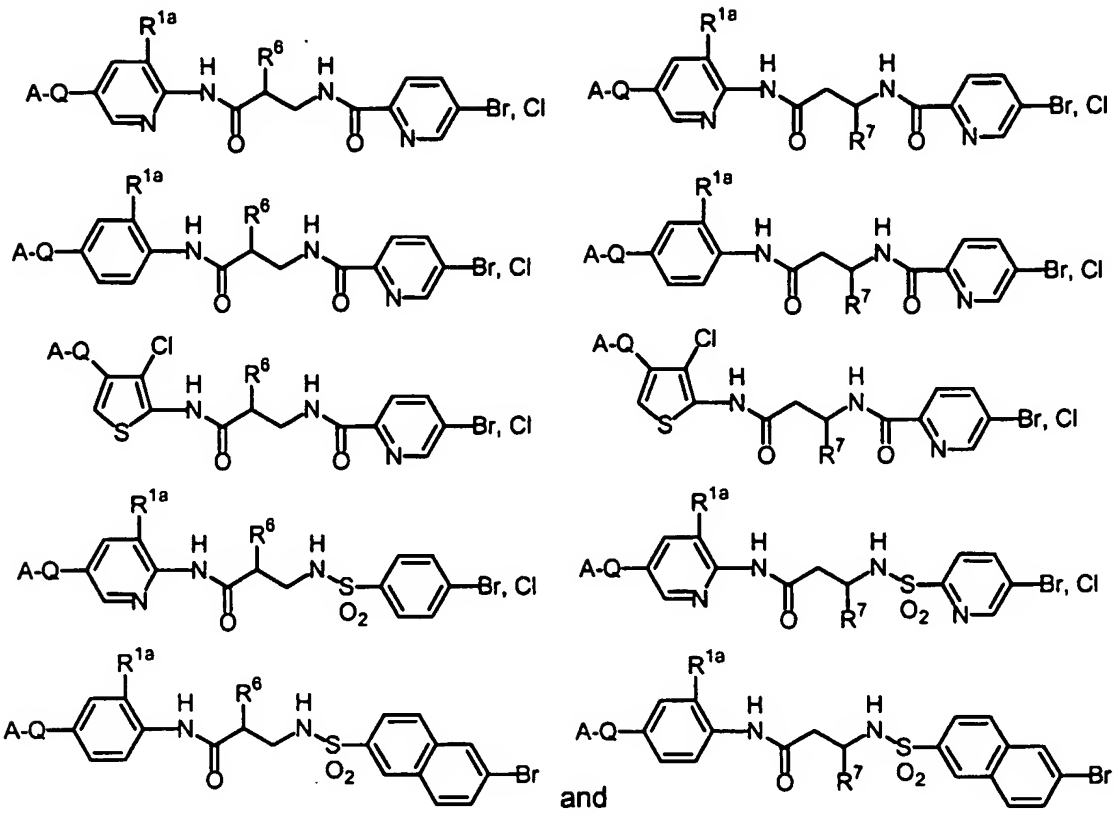
-NH-SO_2-N(-Me)$_2$;

wherein A-Q is a member independently selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives thereof.

9. A compound of claim 1 selected from the group consisting of:



and

wherein R^{1a} is a member selected from the group consisting of:

H; -Cl; -F; -Br; -I; $-NO_2$; -O-Me; -Me; -C(=O)-OH, -C(=O)-O-(C_1-C_6 alkyl), and -C(-O)-NH_2;

R^6 is a member selected from the group consisting of:

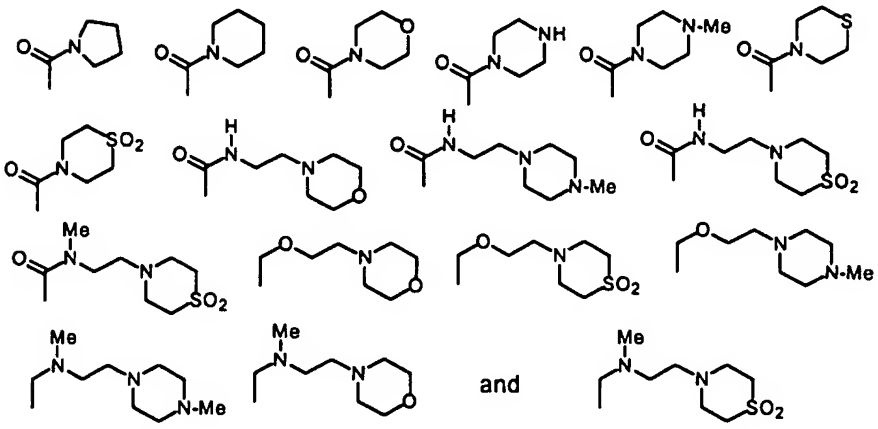
H; $-NH_2$; -NH-C(=O)-Me; -NH-C(=O)-O-Et; -NH-C(=O)-O-Bu; -NH-C(=O)-O-Bn; -NH-C(=O)-NH-Me; -NH-C(=O)-NH-Bu; -NH($-SO_2$)-Me; -NH-SO_2-Me; -NH-SO_2-Ph; -NH-SO_2-NH-Me and -NH-SO_2-N(-Me)$_2$;

R^7 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, -CH_2-COOH;-(-CH_2-)$_2$-COOH; -COO-Et; -C(=O)-NH_2; -C(=O) -N(-CH_3)$_2$; -CH_2-NH_2; -CH_2-N(-CH_3)$_2$;

-CH_2-NH-Ac; -CH_2-NH-SO_2-Me; -CH_2-OH; -CH_2-O-Me; -CH_2-O-Ac;

-CH_2-O-CH_2-CH_2-O-Me; -CH_2-O-CH_2-CH_2-N(-Me)$_2$; and



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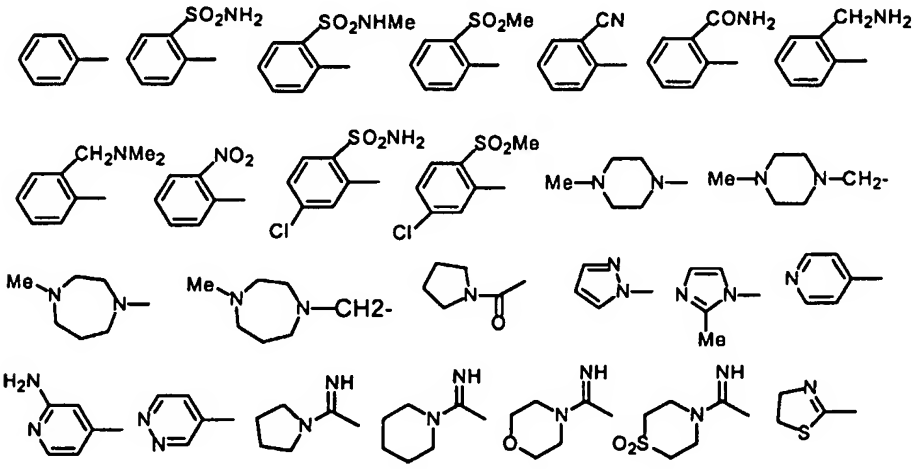
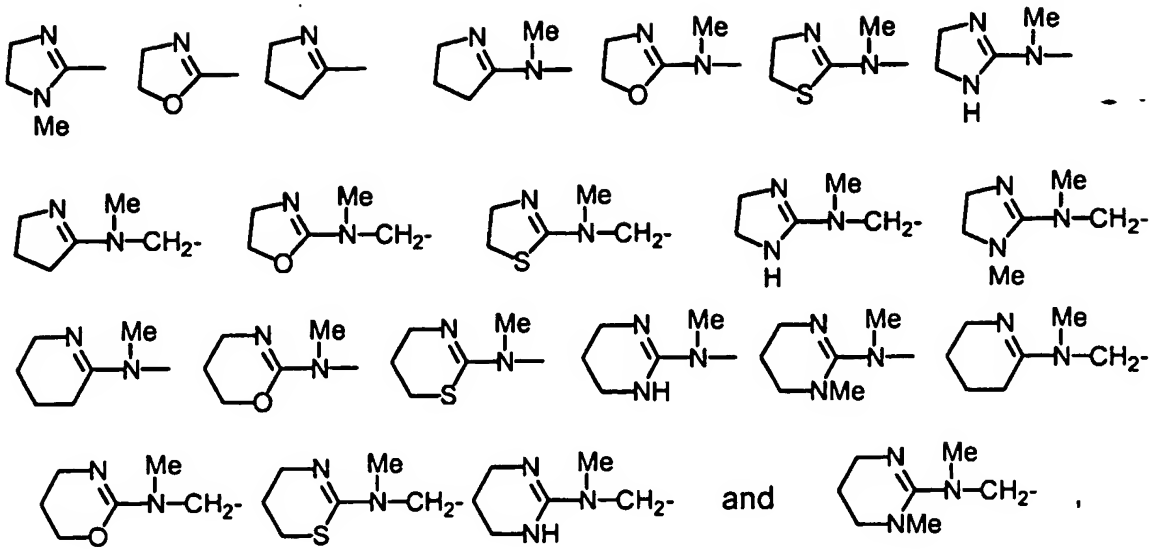
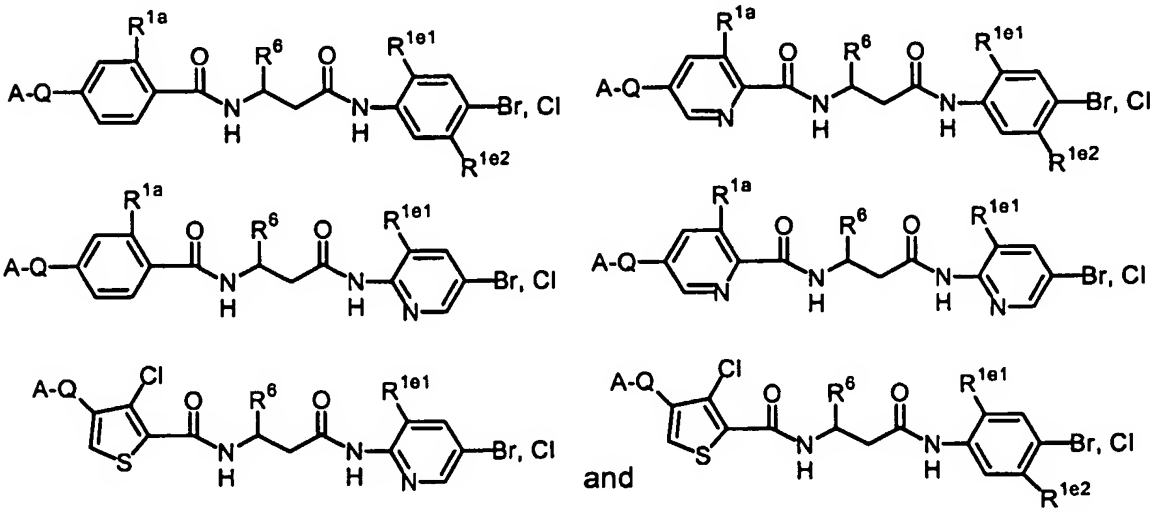
A-Q is selected from the group consisting of:





and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

10. A compound of claim 1 selected from the group consisting of:



wherein:

R^{1a} is a member independently selected from the group consisting of:

H; -Cl; -F; -Br; $-NO_2$; -O-Me; -C(=O)-OH; -C(=O)-O-Et and $-C(=O)-NH_2$;

R^{1e1} is a member independently selected from the group consisting of:

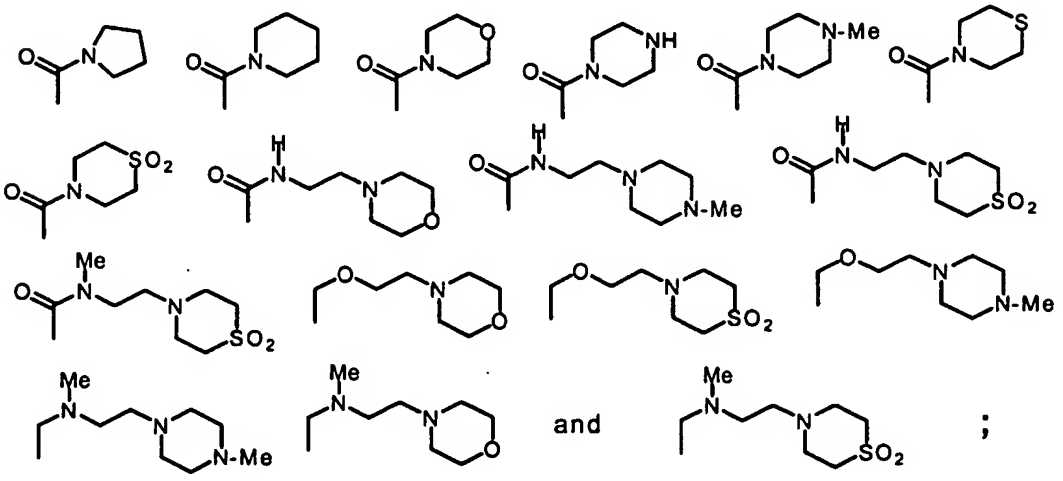
H; -Cl; -Br; -OH; $-NO_2$; -O-Me; $-NH_2$; $-CH_2-NH_2$; -NH-Me; $-CH_2-OH$; $-CH_2-O-Me$; -CN; $-C(=O)-NH_2$; $-C(=O)-NH-Me$; $-SO_2-Me$; $-SO2-NH_2$ and $-SO_2-NH-Me$;

R^{1e2} is a member independently selected from the group consisting of:

H; -Me; -O-Me; -Cl; -Fl; -Br; $-CF_3$; $-C(=O)-NH_2$; -CN; $-C(=O)-OH$; $-C(=O)-O-Me$; $-SO_2-Me$; $-SO_2-NH_2$; $-SO_2-NH-Me$ and $-NO_2$;

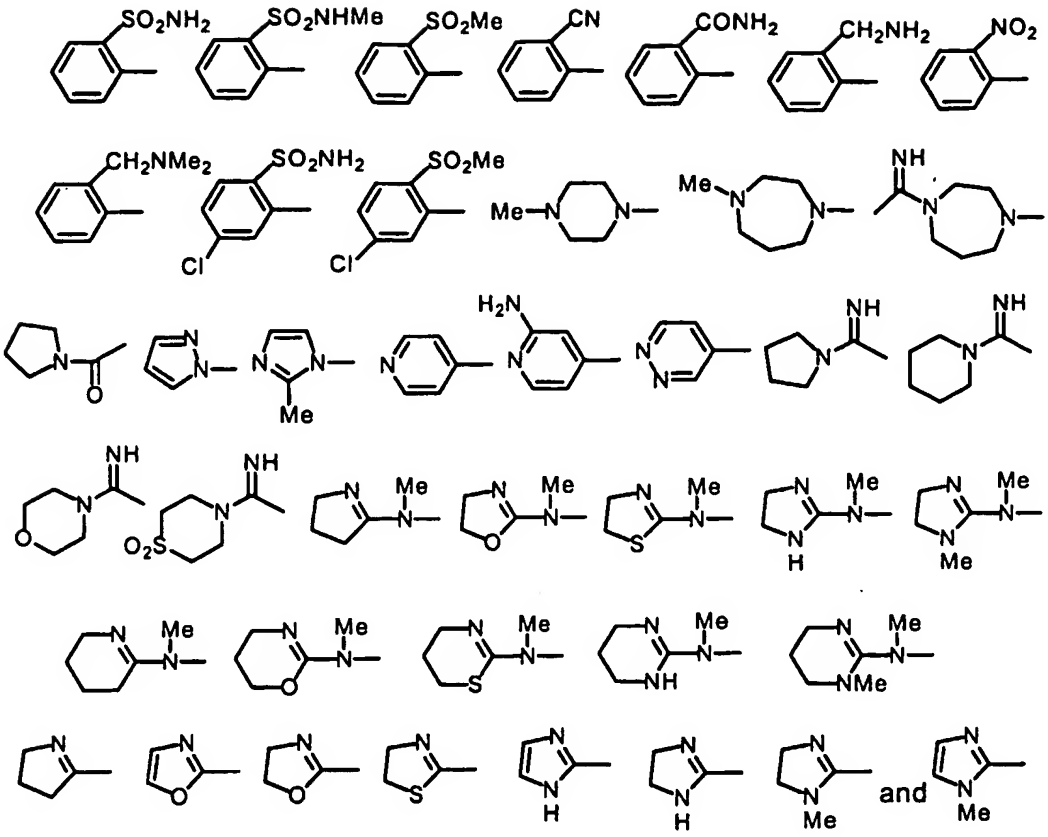
R^6 is independently a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$; -COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$; $-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$; $-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$; and



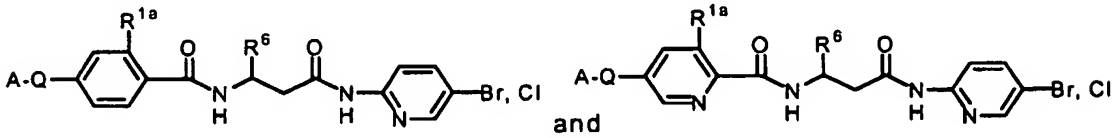
;

A-Q is independently a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

11. A compound of claim 1 selected from the group consisting of:



wherein:

R^{1a} is independently a member selected from the group consisting of:

H; -Cl; -F; -Br; -Me; $-NO_2$; -O-Me; -C(=O)-OH; -C(=O)-O-Me and $-C(=O)-NH_2$;

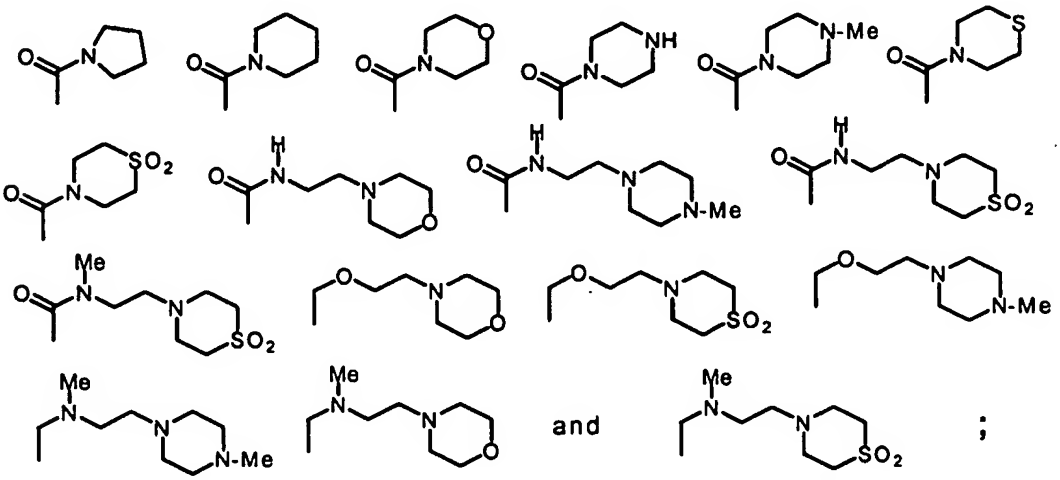
R^6 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2-)_2-COOH$;

-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

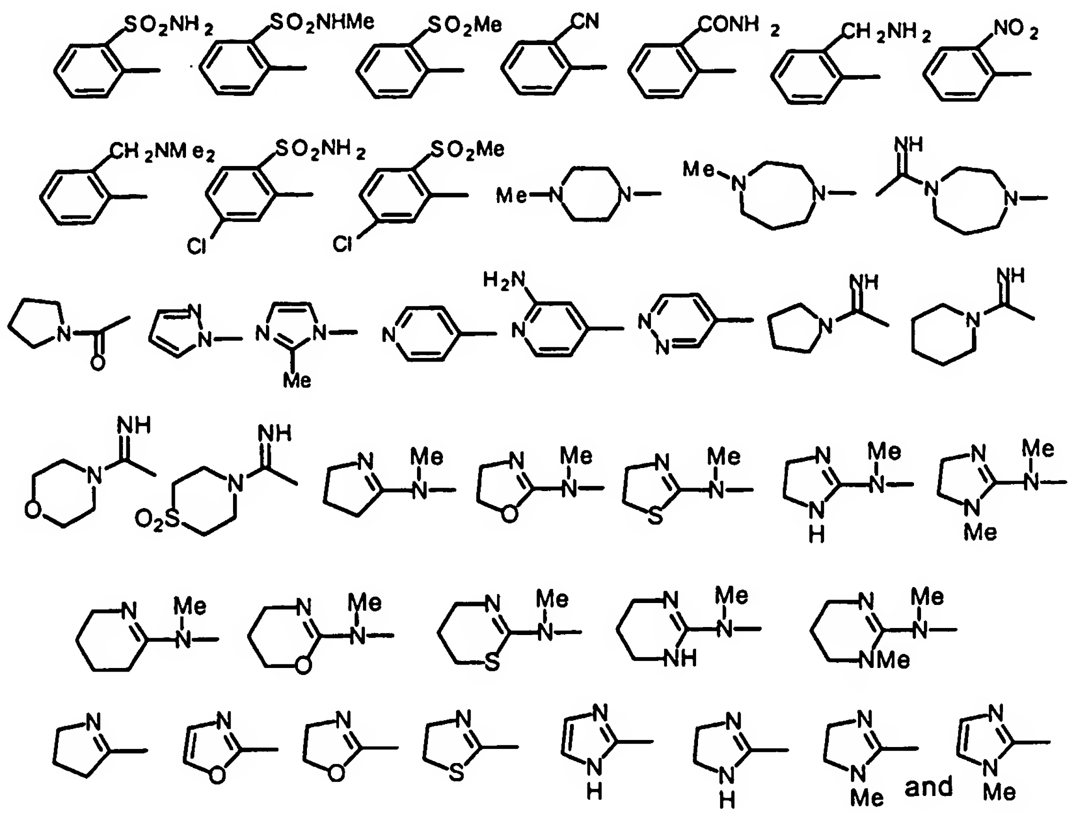
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$; and

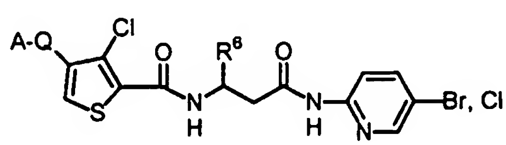


;

A-Q is a member selected from the group consisting of:

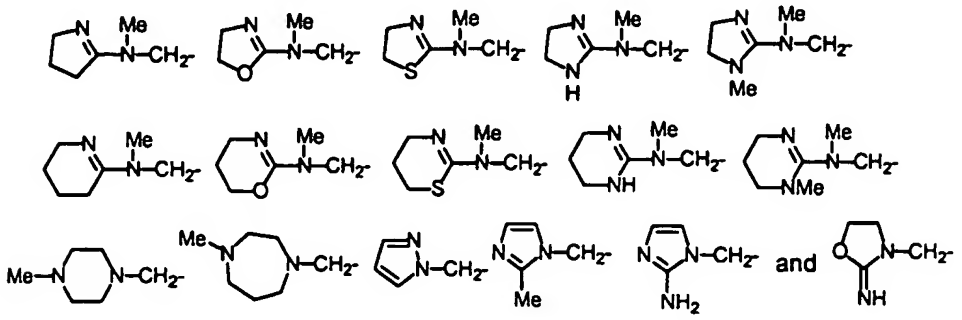


12. A compound of claim 1 having the following formula:



wherein

A-Q is a member independently selected from the group consisting of:



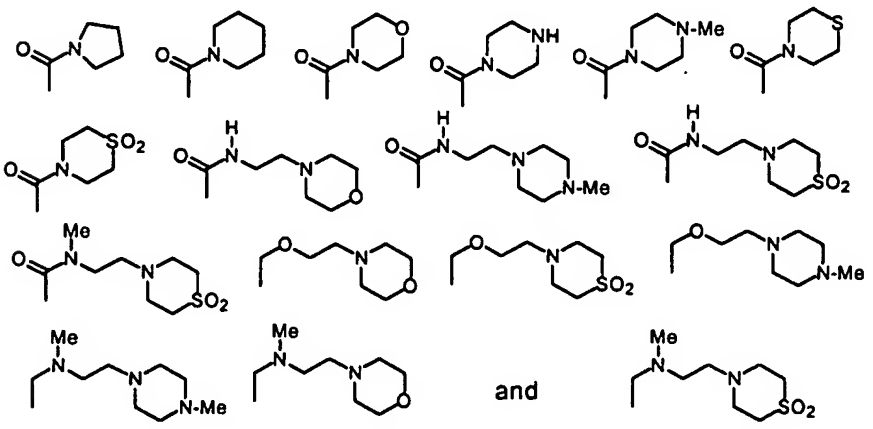
R^6 is a member selected from the group consisting of:

H; -Me; phenyl; benzyl; -COOH, $-CH_2-COOH$;$-(CH_2)_2-COOH$;

-COO-Et; $-C(=O)-NH_2$; $-C(=O)-N(-CH_3)_2$; $-CH_2-NH_2$; $-CH_2-N(-CH_3)_2$;

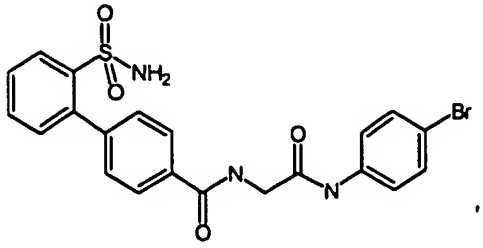
$-CH_2-NH-Ac$; $-CH_2-NH-SO_2-Me$; $-CH_2-OH$; $-CH_2-O-Me$; $-CH_2-O-Ac$;

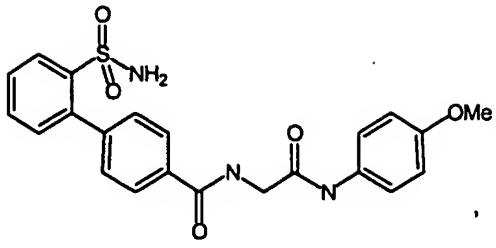
$-CH_2-O-CH_2-CH_2-O-Me$; $-CH_2-O-CH_2-CH_2-N(-Me)_2$; and

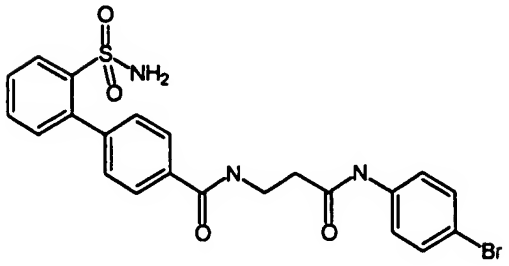


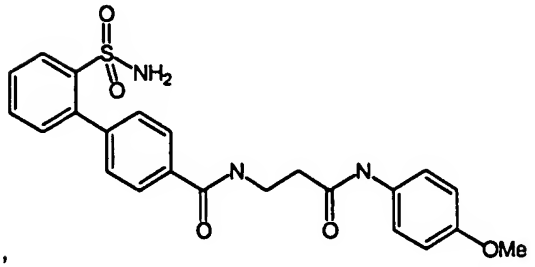
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

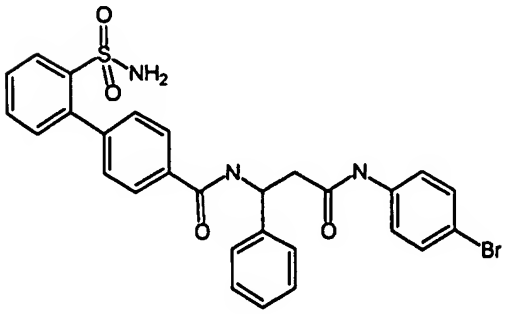
13. A compound of claim 1 selected from the group consisting of:

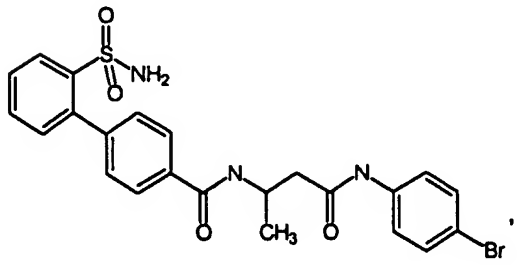


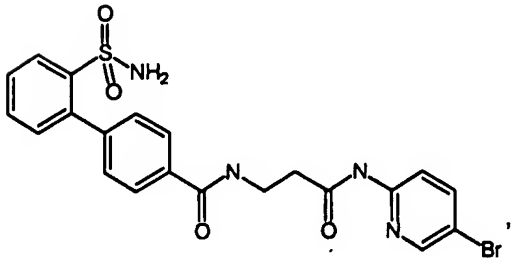


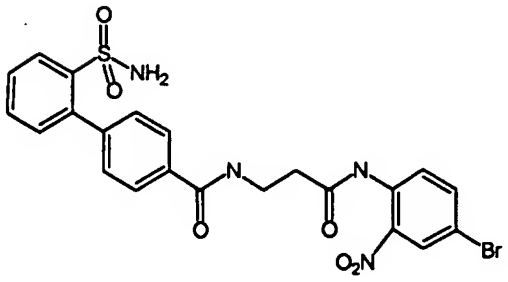












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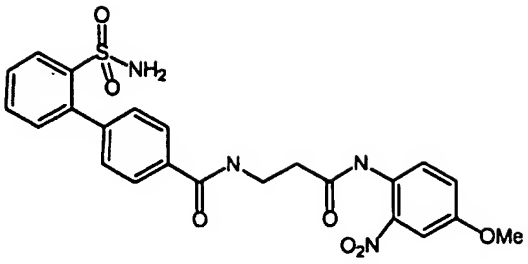

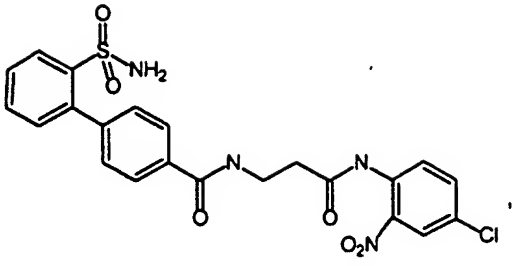

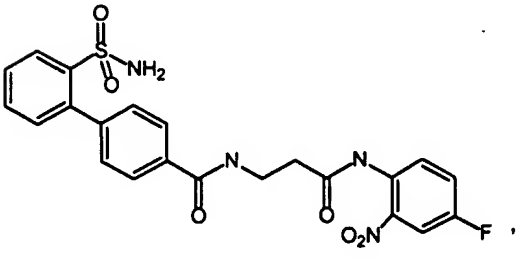

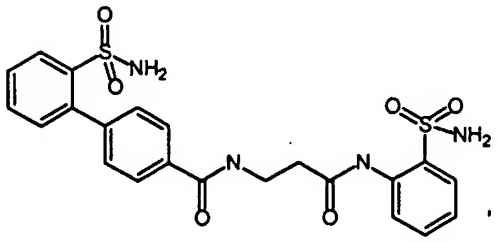

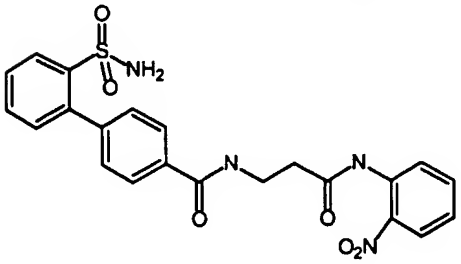

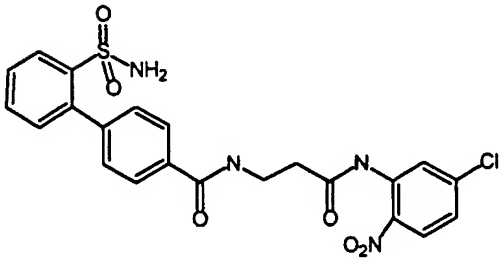

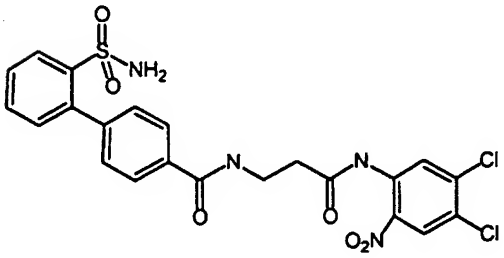

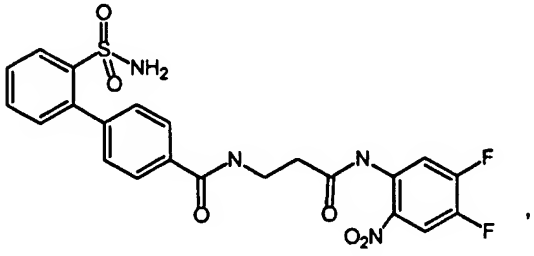

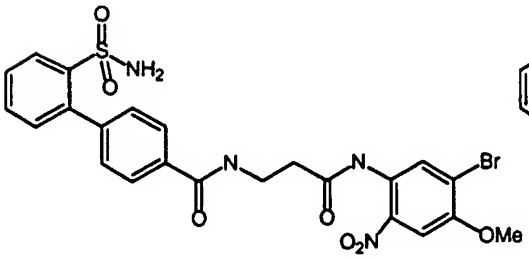

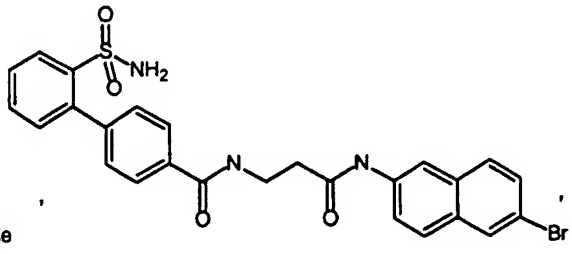

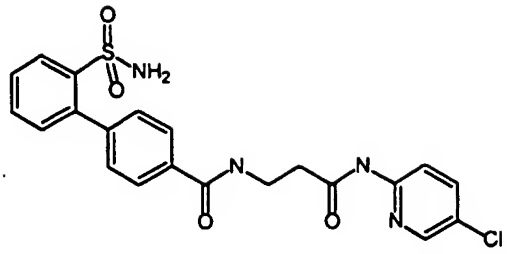

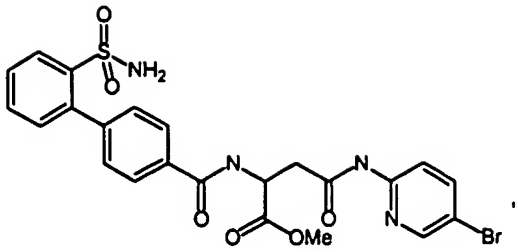

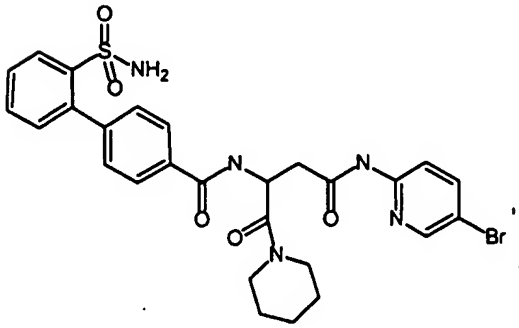

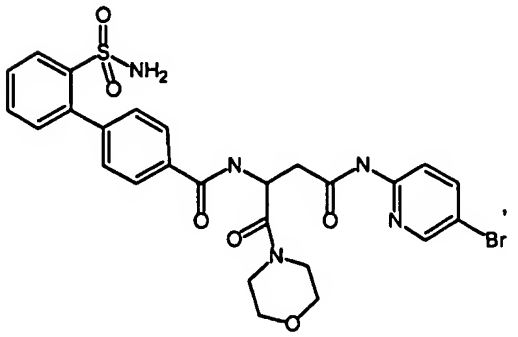

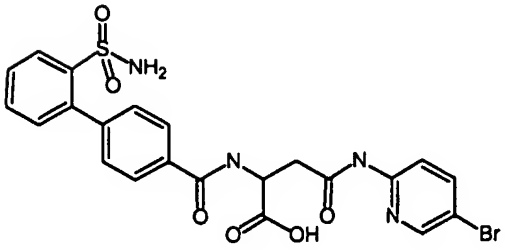

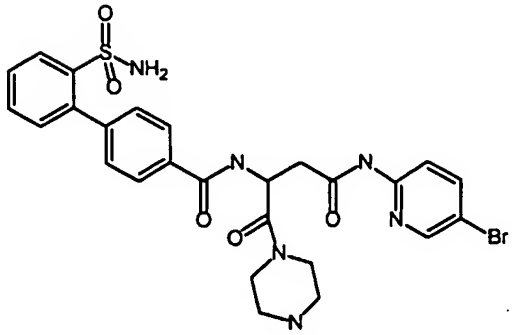

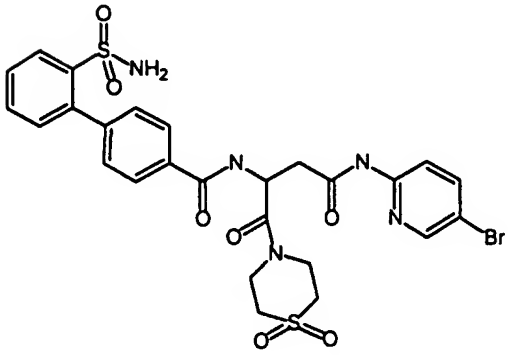

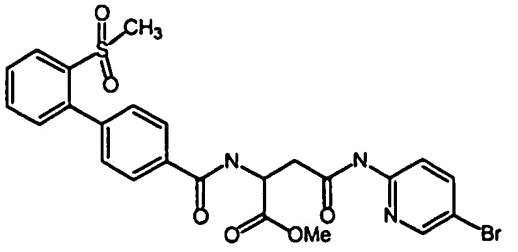

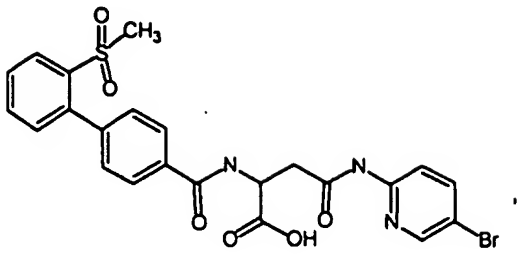

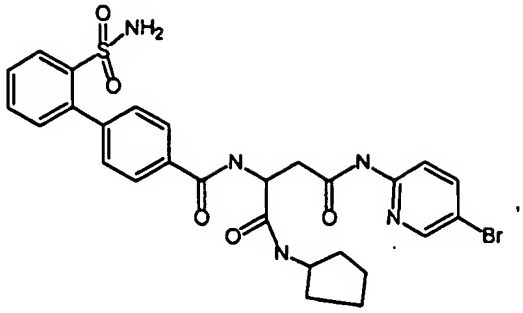

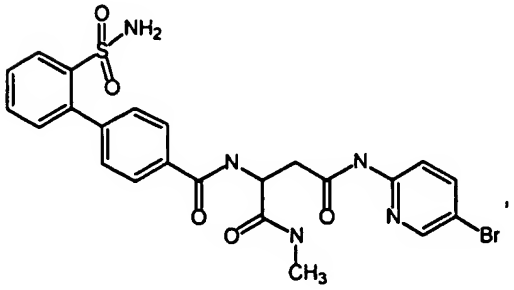

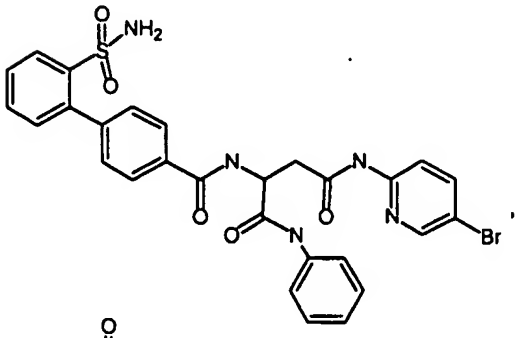

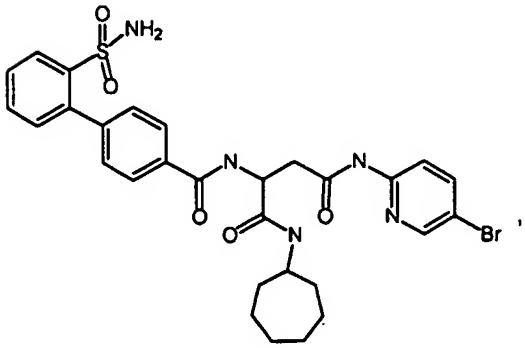

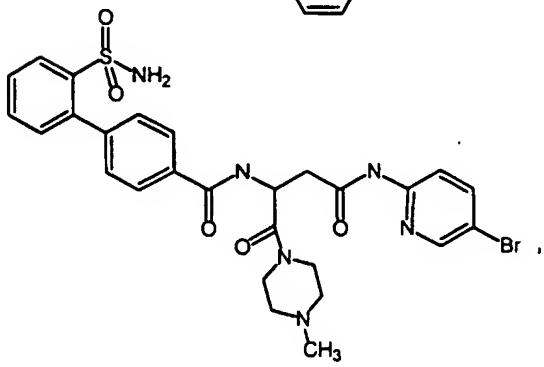

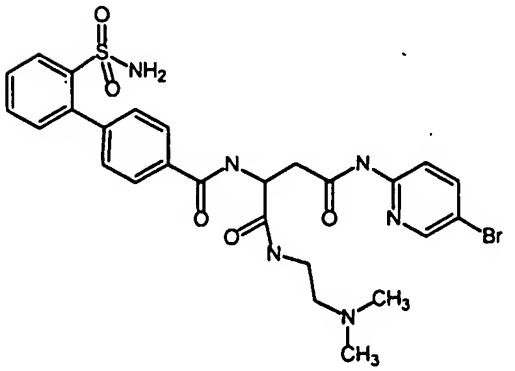

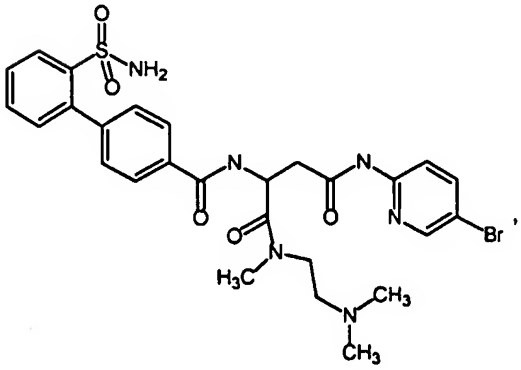

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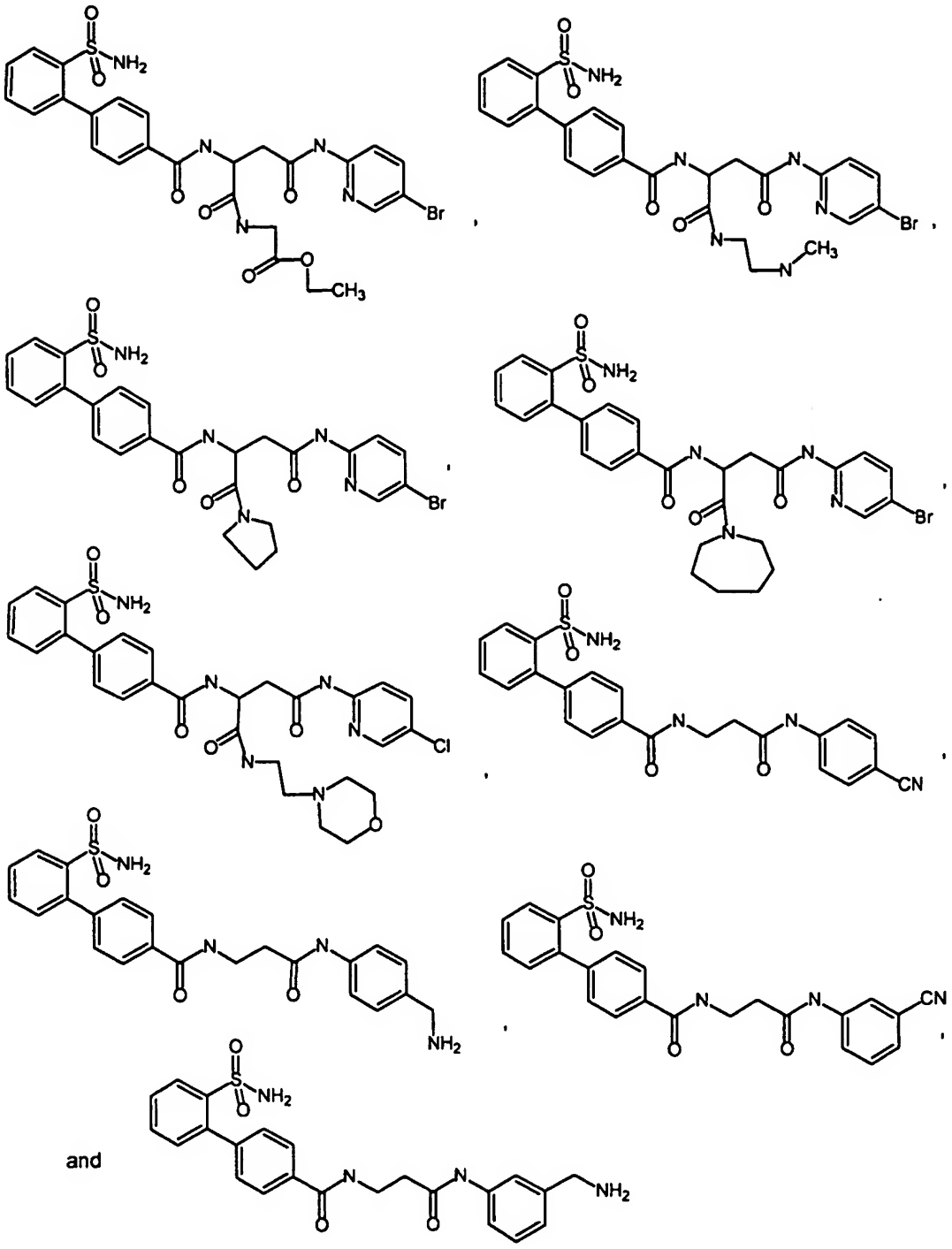

and

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

14. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 1.

15. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

16. The method of claim 15, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

17. A method for inhibiting the coagulation of biological samples comprising the step of administering a compound of claim 1.

18. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of claim 2.

19. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of a compound of claim 2.

20. The method of claim 19, wherein the condition is selected from the group consisting of:

acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

21. A method for inhibiting the coagulation of biological samples comprising the step of administering a compound of claim 2.

INTERNATIONAL SEARCH REPORT

PCT/US 00/31520

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/75 C07D295/18 C07C311/16 C07C311/18 C07D409/12
A61K31/44 A61K31/18 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 71493 A (COR THERAPEUTICS INC) 30 November 2000 (2000-11-30) tables 15-24 tables 51-56 claims; examples 17,21,25,35,38	4-13
E	WO 00 71507 A (COR THERAPEUTICS INC) 30 November 2000 (2000-11-30) page 30; claims	4-13
E	WO 00 71508 A (COR THERAPEUTICS INC) 30 November 2000 (2000-11-30) claims; examples 33-37,40	4-13
A	WO 96 39930 A (MINNESOTA MINING & MFG) 19 December 1996 (1996-12-19) claims; examples 4,5	4-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2001	23.02.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 11657 A (CREW ANDREW PHILIP AUSTIN ;JONES STUART DONALD (GB); MORGAN PHILLI) 11 March 1999 (1999-03-11) page 2, line 20-28; claims	4-13
A	WO 99 32477 A (SCHERING AG) 1 July 1999 (1999-07-01) page 72, line 15 -page 75, line 26; claims	4-13
A	HARTMAN G D ET AL: "Nonpeptide glycoprotein IIb/IIIa inhibitors. 19. A new design paradigm employing linearly minimized, centrally constrained, exosite inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 9, no. 6, 22 March 1999 (1999-03-22), pages 863-868, XP004159618 ISSN: 0960-894X see compounds 14-16 table 3	4-13
A	WO 94 12181 A (MERCK & CO INC ;EGBERTSON MELISSA S (US); TURCHI LAURA M (US); HAR) 9 June 1994 (1994-06-09) page 130-150; claims	4-13
A	WO 95 32710 A (MERCK & CO INC ;HARTMAN GEORGE D (US); DUGGAN MARK E (US); IHLE NA) 7 December 1995 (1995-12-07) the whole document	4-13

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 00/31520

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 15-17 and 19-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [X] Claims Nos.: 1-3 and 14 to 21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3 and 14 to 21

Present claims 1-3 and 14 to 21 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claims 4 to 11.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.